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Division for Clinical Research Resources

Guidelines for the General Clinical Research Centers Program (M01)

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Division for Clinical Research Resources

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INTRODUCTION

The National Center for Research Resources (NCRR) is a "catalyst for discovery." Through NCRR, biomedical investigators supported by the disease-oriented institutes of the National Institutes of Health (NIH) can access the resources and technologies they need to conduct research that improves human health.

The diverse research centers and resources supported by NCRR throughout the Nation include:

- General Clinical Research Centers grants (M01); National Gene Vector Laboratories (U42); Islet Cell Resource Centers (U42); the National Disease Research Interchange (U42); Clinical Research Career Development, including support for Mentored Clinical Research Scholar Program Awards (K12), Mentored Patient-Oriented Research Career Development Awards (K23), and Midcareer Investigator Awards in Patient-Oriented Research (K24); Science Education Partnership Awards (R25); the Rare Diseases Clinical Research Network (U54); Small Business Grants (R41, R42, R43, and R44); and Cooperative Agreements to support meetings (R13, U13);

- biomedical technologies and instrumentation;

- mammalian and nonmammalian models of human disease;

- facility construction and renovation, and support to increase research competitiveness of minority institutions and states with limited NIH funding.

NCRR-supported research centers and resources are cost-effective. Each year, tens of thousands of investigators share in their use. Moreover, while conducting research at these centers and resources, many investigators enter into collaborations with scientists from other disciplines who have complementary skills and projects. These partnerships not only extend research dollars, but also promote the exchange of scientific ideas.

GUIDELINES FOR CLINICAL RESEARCH PROGRAMS
of the National Center for Research Resources, National Institutes of Health

I. DIVISION FOR CLINICAL RESEARCH RESOURCES

The Division for Clinical Research Resources (DCRR) of the NCRR includes four complementary sets of programs: 1.) a national network of General Clinical Research Centers (GCRCs); 2.) a portfolio of regional and national research resources to foster clinical research; 3.) a portfolio of programs to enhance career development in clinical research; and 4.) a program to foster science education. NCRR has been assigned the number 93.389 in the Catalog of Federal Domestic Assistance. GCRC grants carry the activity code, "M01."

II. GENERAL CLINICAL RESEARCH CENTERS

Medical institutions with clinical investigators supported with peer-reviewed funds from NIH and other sources are eligible to compete for a GCRC award to facilitate patient-oriented research in a cost-effective approach. Most institutions with NCRR-funded GCRCs are affiliated with medical schools, but institutions of higher learning devoted to medical research also may apply. Inpatient and outpatient areas of the GCRC must be located in facilities either accredited by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) or certified to accept Medicare and/or Medicaid reimbursement. Academic institutions are encouraged to assign the GCRCs a central, leadership role for all of their patient-oriented research. GCRCs are encouraged to host qualified investigators from other nearby institutions that do not have such a facility.

The GCRCs host both funded studies and pilot studies that may lead to future NIH or other sources of peer-reviewed clinical research grant support. GCRC configurations vary from site to site and reflect the research needs of investigators. An institutional GCRC may include inpatient and outpatient facilities, core or other resource laboratories for radioimmunoassays, mass spectrometry, cell sorting, imaging, sleep studies, and more. GCRC investigations can include studies of normal and abnormal human physiology and studies of the cause, prevention, progression, control, and cure of diseases that afflict individuals of all ages and ethnic backgrounds. Collaborations between basic and clinical scientists are encouraged. The GCRCs also provide a unique environment for mentored training of health professionals in issues related to patient-oriented research. The safety of participants in clinical research is of paramount importance, and the GCRC Program funds Research Subject Advocates (RSAs) in support of this goal.

The essential feature that is common to all GCRCs is the broad range of patient-oriented scientific inquiry. Investigators from research disciplines including medical subspecialties, bioengineering, and the basic sciences are encouraged to take full advantage of research

advances including the rich databases containing important new data on the human genome and novel imaging technologies. Because of the nature of the GCRCs, no single group of investigators or categoric research area may dominate the utilization of the GCRC or use more than one third of the GCRC resources, except for acquired immunodeficiency syndrome (AIDS) studies. In unusual circumstances, a research discipline may temporarily exceed that limit.

Because each GCRC is designed to support the investigator-initiated, peer-reviewed, clinical research projects within the institution, the configuration and available resources of the respective GCRC vary according to the research needs of the investigators. Consequently, either the inpatient or the outpatient activities may predominate in a GCRC. All studies must adhere to NIH policies regarding inclusion of women, minorities, and children; Federal regulations that relate to human subject research (45 CFR 46); and FDA regulations and policies. The priorities of the research to be performed at each GCRC are determined by the local GCRC Advisory Committee (GAC). This committee also anticipates future needs for clinical research within the institution and proposes new initiatives.

The GCRC Program allows flexibility in the design, accessibility, and scope of research. This facilitates rapid initiation of new and novel protocols and pilot studies. The GCRC Program provides financial support for the components essential to clinical research: operating expenditures; hospitalization and ancillary laboratory costs; and salaries of key personnel, including nurses, research subject advocates, research bionutritionists, administrators, core laboratory staff, biostatisticians, and computer personnel. Funds for renovation and equipment also may be provided.

A. Inpatient Area:

The inpatient facility of a GCRC usually is located within a physically discrete unit that contains inpatient rooms and research beds. It also may include administrative offices, a laboratory, research bionutrition area, computerized data analysis facility, and other supporting services required to perform high-quality clinical research. Ideally, the GCRC is in close proximity to other established patient-care units. Supported inpatient research may also include studies conducted in other “scatter-bed” areas, such as psychiatric wards or intensive care units.

B. Outpatient Area:

Clinical research that involves outpatients frequently complements or provides an alternative to inpatient investigations. This type of research may be performed in one of several locations on the inpatient unit, in a separate dedicated GCRC outpatient area, in a regular hospital outpatient clinic, or in another discrete area assigned for GCRC use on a *pro rata* basis. Staffing and space allocations depend on the scope and complexity of the outpatient investigations.

C. Research Subject Advocate:

The primary function of the RSA is to ensure that studies on the GCRC are designed and conducted safely and ethically with protection of human subjects accorded the highest priority. The RSA acts as a liaison with the institutional Offices of Human Protections (or equivalent), including the Institutional Review Boards (IRBs). The RSA develops and guides implementation of policies and procedures for timely and appropriate reporting of adverse events, development and adherence to the Data and Safety Monitoring (DSM) Plan, approval and recording of all protocol amendments and changes in informed consent documents, performance of regulatory responsibilities in a complete and timely manner, and conduct of the research as written in the most recently approved protocol. While the RSA cannot and should not take on the above responsibilities of others, he/she will monitor activities on the GCRC and recommend appropriate corrective action if deficiencies are found. The RSA should be informed of all issues related to human subject protection on the GCRC. In addition, the RSA should receive copies of all correspondence to and from the IRB, FDA, and the sponsor related to conduct, safety, clinical holds, removal of holds, changes, and other relevant information concerning protocols on the GCRC. The RSA should provide educational and training opportunities for GCRC staff on human subject protection. The RSA should reflect the views of the research participants to GCRC staff when appropriate.

The RSA works closely with and keeps the Program Director (PD) and GAC informed of activities related to human subject safety and protection on the GCRC. However, the RSA reports to the Principal Investigator (PI) of the GCRC grant and not to the PD or GAC. This reporting structure ensures that the RSA has the appropriate independence from those involved in the design, approval and conduct of studies and implementation of activities related to human subject protections.

D. Core Laboratories:

The primary functions of a Core Laboratory are to provide sophisticated support to ongoing GCRC protocols and to develop or validate new methods. In addition, the laboratories may provide clinical research training for investigators.

Core Laboratory requirements vary widely. Some GCRCs may not need a full Core Laboratory; rather, only a small sample-processing area may be required. Laboratory equipment, supplies, and personnel supported through the GCRC grant serve several investigative groups. Under special circumstances, a test for a single group of investigators may be supported if it is within the Core Laboratory's capabilities and is critical to conduct an investigation of high scientific merit and program relevance.

In general, routine tests, such as blood chemistries, hematologic determinations, and urinalyses,

that are available in the hospital's clinical chemistry laboratories or in another Medicare-approved clinical chemistry laboratory are not performed in the GCRC Core Laboratory; rather, they are supported through ancillary funds. However, such tests may be performed in the GCRC Core Laboratory when this is critically important for timeliness, when an extreme degree of accuracy is needed, or if patient safety is at stake. Cost sharing of Core Laboratory functions should be sought from funded investigators.

Core Laboratories may specialize in, but are not limited to, areas such as exercise physiology and body composition, mass spectrometry, magnetic resonance imaging, ultrasound, positron emission tomography, tissue culture, cell biology, molecular genetic analyses of DNA obtained from patient material, and cell and gene therapy.

Core Laboratories are encouraged to make their areas of specialized expertise available to other GCRCs. Records of such services and collaborations should be kept, as they may be helpful in justifying continued support of the laboratory. See below (Section IV-G-11) regarding Program Income.

The GAC is responsible for reviewing the Core and other resource Laboratories to ensure that the activities are serving the research needs of a wide array of investigators, that laboratory tests are not routine, and that priorities are set for the use of the Laboratory when concurrent demands exceed the Laboratory's capacity. In all cases, NIH-supported investigations are to be given the highest priority.

E. Informatics Core:

A clinical investigator must be able to publish his/her scientific findings. This requires that data be 1.) collected accurately, 2.) monitored appropriately, 3.) secured, 4.) managed effectively, and 5.) accessible for analysis and reporting. The mission of the Informatics Core is to provide the information infrastructure necessary to accomplish this.

For a GCRC to be successful and efficient, information flow between the GCRC Cores must be both timely and accurate. The Informatics Core interacts with the other GCRC Cores, integrating the information needs of the Center. The Informatics Core should facilitate the secure and confidential sharing of scientific data between GCRCs. The Informatics Core should provide leadership in exploring and implementing new technologies to stimulate and promote clinical research. The Informatics Core should provide education and training in the use of information technologies and research data management to the GCRC staff and research teams.

The requirements of the Informatics Core will depend on both the specific needs of the GCRC and the existing institutional resources. In all cases, each Informatics Core should have a file server to comply with current and anticipated NCRR bioinformatics goals to communicate

within and between GCRCs. The file server should meet standards for the secure storage, archiving, management, and analysis of protocol data. A network should be in place to facilitate GCRC operations and investigations associated with all GAC-approved studies. The Informatics Core should ensure that GCRC network facilities are accessible to all GCRC Core components and promote the adherence to data management standards. The Informatics Core also should provide or facilitate ongoing training and education in the use of its resources.

The GAC is responsible for reviewing the Informatics Core activities to ensure that the research needs of a wide array of investigators are being served. The GAC will prioritize the use of the Informatics Core resources when concurrent demands exceed capacity, with NIH-supported investigations being given the highest priority. Initiatives that may have a substantive impact on the Informatics Core should be presented to the GAC for review and approval.

F. Bionutrition Core:

Not all GCRCs require a Bionutrition Core. When present, it facilitates and implements the nutrition components of GCRC protocols. It may be involved in one or more of the following functions: assisting investigators with nutrition aspects of research design, implementation, data collection and analysis; implementing controlled feeding studies (via meals prepared on site or outsourced as appropriate) and metabolic studies, as well as facilitating and monitoring subject nutrition compliance; performing nutrition and nutrient intake assessment; conducting anthropometric, body composition, calorimetry and other physiologic and metabolic measurements; providing personnel administration, metabolic kitchen operations, food procurement, production and service; and educating and training professional and non-professional staff, study participants, students and the public.

G. Principal Investigator:

The PI of a GCRC is required to commit at least one percent time effort to the M01 grant; however, he/she derives no salary support from the grant. He/she is an individual familiar with human subjects research whose authority transcends departmental lines--for example, the Dean of the medical school. Requests for an exception will be reviewed on a case-by-case basis. The PI has the ultimate responsibility for the administration and operation of the GCRC and is the person with whom NIH communicates on broad institutional matters relating to the GCRC grant. The DCRR should be notified immediately, in writing, when a change in PI is planned. The letter should include the curriculum vitae of the proposed individual. The PI appoints the PD and members of the GAC (see Section II-H) and is responsible for the development of the GCRC as an institutional resource. Should the PI determine that a new PD is needed for the GCRC, he/she is responsible for seeking approval from NCRR for such a change. This request should be accompanied by a current curriculum vitae and information regarding existing sources of peer-reviewed research support; the request is to be cosigned by an authorized institutional

business official and the PI.

H. Institutional GCRC Advisory Committee (GAC):

The GAC usually consists of 8-12 members, appointed by the PI, on a rotating basis. This Committee is responsible to the PI. It should be composed of a cross-section of faculty members who are familiar with the broad range of the GCRC research activities. The GAC shall not be chaired by the PD or Associate/Assistant PD. Individuals receiving salary support from the GCRC grant shall not be voting members of the GAC. The GAC supervises and reviews all operations of the GCRC, its Core Laboratories, Informatics Core, and other components; sets general policies; delineates common needs of the GCRC investigators; establishes admission policies; and evaluates projects for GCRC use. Studies on the GCRC must have GAC approval. This approval must be obtained prior to initiation, except when temporary approval has been given by the PD or his/her designee and the IRB for urgent studies created by an unexpected opportunity to study unusual research patients; these studies will be reviewed by the GAC at its earliest meeting.

The GAC should prospectively prioritize projects for GCRC use to assist the PD in allocating resources. In all cases, NIH-funded clinical research must be given preference. The GAC is responsible for ensuring implementation of existing NIH policy on the inclusion of women, minorities, and children as study subjects and for approval of DSM plans for all GCRC protocols. In addition, the GAC shall determine if a protocol involves significant risk, and if so, will evaluate and approve the required Data and Safety Monitoring Board (DSMB). The GAC must also designate for each protocol, the category of inpatient research days and outpatient visits as Category A, B, or D. For appropriate classification of industry-related projects, the GAC may request additional materials. The GAC must review copies of the research agreement between the investigator and industry, an itemized budget, and other relevant correspondence, detailing the drug or other therapeutics or devices supplied.

The GAC should review periodically all GCRC operations to ensure that GCRC resources are used for the most scientifically justified and relevant projects. Each year, a copy of the GCRC's Annual Progress Report shall be supplied to each GAC member and shall be reviewed at a subsequent GAC meeting. The GAC should encourage junior faculty members to perform clinical research and assist them in applying appropriate concepts and methods. Meetings of the full GAC should be held at least quarterly, and detailed records must be kept. The minutes of the GAC meetings are examined at the site visit when the GCRC grant application is reviewed. The GAC may form subcommittees to carry out some of its functions, which may include the review of biostatistical design of projects, ethical concerns, or the assignment of priority scores based on scientific merit as well as their need for GCRC resources.

The GAC should include a biostatistician both to assist with the review of project design and to

optimize subsequent data analysis.

The GAC is to work closely with the PD to proactively address investigator resource needs, encourage GCRC use by investigators at the institution who are not currently using the resource, and provide outreach to investigators from institutions without a GCRC or comparable resources.

The GAC shall oversee the GCRC budget. All requests to NCRR for funds (competitive renewal, noncompetitive renewal, supplements) shall be endorsed by the GAC prior to submission of the request to NCRR. Once funds are awarded, all significant rebudgeting shall be endorsed by the GAC. During the grant year, the GCRC PD and Administrative Manager are to work closely with the GAC and provide systematic updates on financial matters including: comparison of projected expenditures with actual expenditures to date; and actual use to date of GCRC resources (inpatient days, outpatient visits, ancillaries) by specific protocols. In addition, the GCRC PD and Administrative Manager are to report to the GAC on apparent unmet needs of investigators, career development and other related activities, and other topics relevant to the host institution.

The minutes of the GAC meetings shall document all reports to the GAC and all recommendations made by the GAC.

I. Institutional Review Board for Human Research:

All GCRC research projects must be reviewed and approved by an IRB to ensure protection of the rights and welfare of research subjects. (See 45 Code of Federal Regulations 46.) The IRB must have registered with the Office for Human Research Protections and have completed a Federalwide Assurance. The composition of the IRB and its attendance records and minutes are examined at the site visit when the GCRC grant application is reviewed. All research projects must also be approved by the GAC. Documentation of IRB approval of protocols, as well as copies of currently approved consent forms, must be maintained in the GCRC administrative files. "IRB approval" means full, final IRB approval. In addition, all GCRC protocols must comply with all applicable Federal and State regulations.

J. Grant-Supported Personnel:

The personnel positions that may be supported by GCRC grants are listed below. (See Section IV-B for allowable costs.) The number of positions supported in each category depends upon the size and complexity of the GCRC, recommendations of the NIH peer-review system, and NCRR program priorities. No portion of the salary of the PI may be supported by the GCRC grant.

1. **Program Directorship:** The PD is a senior physician-investigator and a medically licensed, full-time member of the institution's faculty who derives a portion of his or her salary from the GCRC grant for administration of the GCRC. The PD reports to the PI and works closely with the GAC. Furthermore, the PD should be a productive clinical investigator who holds independent peer-reviewed research support and has active GCRC-based protocols. In the event that a PD loses all independent peer-reviewed research support, up to two years will be allowed for submission of grant applications and subsequent funding. If the PD still does not have independent peer-reviewed research support by the end of that time, the PI must nominate a new PD. "Independent peer-reviewed research support" as described herein, is not limited to NIH support; other sources of peer-reviewed support will satisfy this requirement.

   The PD's activities include supervision of GCRC nursing, bionutrition, paramedical, and administrative staffs, and the organization and operation of the Core Laboratories, Informatics Core, and Bionutrition Research area. The PD must be familiar with all GCRC research projects and ensure that the research is carried out as approved by the local IRB. Support for a PD from the GCRC grant ordinarily is limited to a maximum of 0.50 full time equivalent (FTE). Requests for an exception will be reviewed on a case-by-case basis. The PD should provide a focus through which clinical research skills are taught to medical students, house staff, fellows, K12 and K23 awardees, and other junior faculty members. In addition, the PD is expected to be an expert clinician who can command respect and instill the highest standards of clinical research and medical care in the GCRC staff and investigators.

   Most GCRCs will require additional administrative oversight from Associate and/or Assistant Directors. The Associate PD should be a licensed physician and full-time faculty member who is currently conducting research on the GCRC and holds peer-reviewed research support. Support provided to an Associate PD from the GCRC grant may reach a maximum of 0.50 FTE, as long as the individual is either a PI or co-investigator on either an NIH grant or another significant source of peer-reviewed funding. If an Associate or Assistant PD loses all peer-reviewed grant support, that individual will be allowed two years to become a PI or co-investigator of a peer-reviewed grant. If the individual is unsuccessful at the end of that time, either a new Associate/Assistant PD shall be appointed, or the level of support from the GCRC grant will be reduced to 0.25 FTE or less. An Associate PD usually assists the PD in the administrative oversight of the Center; this includes the quality of inpatient and outpatient medical care, nursing, paramedical, Core Laboratory, and research bionutrition staffs. The Associate PD may supervise an inpatient or outpatient satellite facility apart from the main GCRC and commonly assists the PD in teaching clinical research methods to medical students, house staff, fellows, and faculty. The total level of Program Directorship reflects the level of GCRC research activity and its complexity.

2. **Administrative Support:** The Administrative Director/Manager is a skilled specialist, responsible to the PD for the day-to-day management of GCRC administration, fiscal matters, and records of GCRC activities. He or she maintains the statistical and financial data needed by the grantee institution, the NCRR Office of Grants Management (OGM), and for inclusion in Annual Reports to NCRR. In the interest of GCRC efficiency, the PD may delegate some administrative authority in non-scientific and non-healthcare delivery matters to the Administrative Director/Manager. A GCRC may use the title "Administrative Director" or "Administrative Manager."

   If warranted by the size of the GCRC, a full- or part-time Administrative Assistant may be supported to perform duties related to GCRC operations, such as maintaining GAC meeting records and consent forms. Administrative Assistants are not supported from GCRC funds to prepare renewal applications or to provide support for developing scientific publications for the PD or other investigators. In general, Facilities and Administrative (F&A) costs provided to an institution by the grant support clerical assistants who prepare grant applications and manuscripts for publication.

3. **Core Laboratory:**

   a. **Core Laboratory Director:** A Core Laboratory Director may supervise the Core Laboratory operations if the scope and sophistication of the laboratory procedures justify such a position; otherwise, the laboratory is supervised by the PD or Associate PD, often through a senior laboratory technician. A Core Laboratory Director is an individual with an advanced degree who may also provide training in sophisticated laboratory techniques to GCRC-based investigators, their laboratory personnel, junior faculty, or fellows. This position usually requires only a small fraction of an FTE. A larger portion of a Core Laboratory Director's time may be required in the initial establishment of complex laboratory procedures, with a smaller fraction of the Laboratory Director's time being required for routine laboratory activities. When there are multiple Core Laboratories with different functions (e.g., body composition core, mass spectrometry core), the GCRC grant may support a fraction of an FTE for the Director of each core.

   b. **Core Laboratory Personnel:** The Core Laboratory staff must possess the expertise needed to provide reliable and accurate analyses required by GCRC research activities.

   c. **Quality Control and Confidentiality:** The GAC must assure that quality control and confidentiality are maintained in compliance with existing Federal and local requirements, such as the Clinical Laboratory Improvement Act.

4. **Nursing:**

   a. **Head Nurse/Nurse Manager:** The Head Nurse/Nurse Manager is responsible for the administrative organization of the GCRC nursing staff (cost-effective staff distribution), training, patient care delivery, and interaction with investigators to ensure that research projects are carried out as approved by the IRB and the GAC. The Head Nurse/Nurse Manager should have a Bachelor of Science degree in Nursing, must be licensed within the state, and have staff privileges within the hospital where the GCRC is located. GCRCs that have many complex projects or a large number of outpatient research visits may require an Associate Head Nurse/Nurse Manager to assist in providing the research patient care needs. That individual should have an educational background and nursing experience comparable to that of the Head Nurse/Nurse Manager of the GCRC.

   b. **Nursing Staff:** The GCRC nursing staff should be trained to make complex research observations and perform precise collections of specimens, while providing exemplary patient care. The professional level and number of nursing personnel required for a GCRC are determined by the size of the unit, the number of research inpatient days and outpatient visits, and the complexity of the research and medical care performed on the GCRC. All nurses must be licensed and have staff privileges either at the hospital where the GCRC is located, at a satellite, or at a scatter-bed unit. Except for the smallest Centers, support of either a full- or part-time Ward Clerk, Unit Manager, or Unit Secretary is appropriate.

5. **Bionutrition Research:**

   a. **Bionutrition Research Manager:** Those GCRCs that have metabolic or other protocols that demand sophisticated nutritional support may justify a position for a Bionutrition Research Manager. This person should have at least a Bachelor's degree and be a registered dietitian. The Bionutrition Research Manager oversees the GCRC dietary staff and works closely with both the nursing staff and GCRC investigators. Up to 1.0 FTE may be supported.

   b. **Nutrition Staff:** Nutritional assessments and the preparation of controlled diets for research subjects require special skills and meticulous attention to detail. To provide the research subjects and investigators with optimal service, the bionutrition staff should be assigned exclusively to the GCRC. The staff number and professional level are determined by the nature of the research, the number of research patients requiring dietary control, and the complexity of the nutritional studies.

6. **Informatics Core:** The Informatics Core Manager is responsible for its overall operation.

Due to the evolving nature of information technology, the Informatics Core Manager should work closely with the PD to ensure that current technologies are employed to meet the GCRC's goals. The Informatics Core Manager should be competent to assist in the organization and analysis of research data and be familiar with the broad array of basic methods of data analyses. He/she must ensure that the tasks necessary to achieve the goals of the Informatics Core are implemented, including:

a. Work with GCRC investigators to further patient-oriented research.

b. Instruct GCRC staff and investigators in the use of Informatics Core resources.

c. Facilitate the dissemination of information within and outside of the GCRC.

d. Work with the biostatistical staff on GCRC-approved protocols.

e. Supervise network and data security to ensure the proper operation and maintenance of GCRC computer hardware and software.

f. Develop and maintain a strategic plan for the Informatics Core.

The minimum qualifications for the Informatics Core Manager include a Master's degree or formal training in research methods and 2 years of experience in application development or computer/network management.

Additional Informatics Core staff may be employed when needed to fulfill the goals of the Informatics Core.

7. **Biostatistician:** The GCRC Biostatistician should hold a doctoral degree in biostatistics or statistics, or have comparable training and experience. The GCRC Biostatistician should have experience in the planning, design, and evaluation of clinical research. The GCRC Biostatistician reviews all protocols and advises the GAC prior to the GAC approval of the protocol. The GCRC Biostatistician consults, and may collaborate, with investigators on study design, implementation, analysis, interpretation, and dissemination of results. He/she should develop new statistical methods as needed for specific projects and train clinical researchers in the principles of study design and analysis. Total support of up to 1.0 FTE will be provided to a GCRC for this individual or other biostatisticians working under his/her direction.

8. **Research Subject Advocate (RSA):** The GCRC shall include funding for a position called "Research Subject Advocate" or similar title. The RSA works closely with the PD and the GAC; however, the RSA shall be directly responsible and report to the PI of the

GCRC grant or his/her designee. The designee must be a high ranking official in the institution with an understanding of clinical research and free from conflicts with the independent role of the RSA. Examples of conflicting roles include the PD, Assistant or Associate PDs, chair of the IRB, or official with overall responsibility for the institution's Human Subjects Protection Office. The RSA is to have appropriate training and experience within the clinical research arena. The RSA may hold an M.D. degree, but appropriately trained Ph.D.s, pharmacists, research nurses, or others also qualify; however, appropriate expertise in clinical research and human subjects protection is necessary. Depending on the needs at the GCRC site and its satellites, more than one FTE may be required for these activities. The RSA duties may be divided among two or more qualified individuals. However, one individual must be designated the Principal RSA. In addition, the GCRC grant may support a Program Administrative Assistant to assist the RSA with effort reflecting the GCRC activity. The effort of the RSA funded through the GCRC grant must be dedicated exclusively to the GCRC activities.

The primary function of the RSA is to ensure that all studies conducted on the GCRC, including all research types, categories, and sites, are designed and conducted safely and ethically with protection of human subjects accorded the highest priority. The RSA assists GCRC investigators, nurses, and other GCRC staff in the safe and ethical conduct of GCRC studies through education, consultation, and enhanced communication and coordination among all members of the team. In addition, the RSA develops and implements policies and procedures to facilitate protection of GCRC human subjects. The RSA provides monitoring and oversight, which includes, but is not limited to, assuring timely and appropriate reporting of adverse events to all required parties, full implementation and adherence to the protocol DSM plan, and that the research is carried out in compliance with the most recently IRB-approved protocol. If deficiencies are found, the RSA recommends or implements corrective action as appropriate.

The RSA assures that all GCRC protocols have GAC-approved DSM plans that are commensurate with the risks to human subjects. The RSA may provide input to the investigator on the design and content of the DSM plan and review proposed DSM plans of all protocols prior to the presentation for approval by the GAC. For those protocols that are of significant risk to be performed on the GCRC, the RSA ensures that the required Data and Safety Monitoring Board (DSMB) is constituted and approved by the GAC prior to start of activities related to this protocol. The RSA may establish and manage but not sit on a DSMB for these studies, but this is not required. The PI of the protocol is charged with the responsibility for establishing a DSMB in cases where no appropriate DSMB is available.

The RSA assists research participants in understanding clinical research and what role they play; however, protocol-specific questions require the participation of the investigator and

research team. In addition, the RSA reflects the views of research participants on GCRCs as appropriate.

9. **Clinical Associate Physician (CAP) and Minority Clinical Associate Physician (MCAP) Programs:** Previously, CAPs and MCAPs were funded as competitive supplements to a GCRC (M01) grant. The K23 mechanism has replaced those supplements; K23s are funded directly, not as supplements to an M01 grant.

10. **Medical and Dental Students:** The GCRC grant may provide support for a "Mentored Medical Student Clinical Research Program," whereby a medical or dental student could take time off from medical school to engage in a mentored program of up to one year of supervised participation in clinical research, didactic coursework related to patient-oriented research, and/or acquisition of laboratory skills that can be applied to patient-oriented clinical research efforts. Support from the GCRC grant may cover up to $20,000 in salary for each awardee, plus up to $5,000 for other relevant expenses. Selection of the recipients should be based on a competitive review by the GAC or another committee constituted for this purpose. Information about the activities of students supported from these funds is required in the GCRC Annual Reports. The GCRC may rebudget, with GAC and institutional prior approval, unrestricted GCRC grant funds for this purpose. The GCRC may also request additional funds for this purpose. In the latter case, the GCRC site is to provide the DCRR its guidelines including: eligibility of students and mentors; selection criteria of the student-mentor pair; and the student's plan for research, didactic coursework, and/or acquisition of laboratory skills. The evaluation plan of the local program is also to be provided. Subsequent support for this program will be reviewed as part of the competitive renewal of the parent GCRC grant.

K. Provisions for Medical Care:

1. **General:** All GCRC research subjects must receive optimal medical care. It is the responsibility of each PI to ensure that appropriate care is provided to patients participating in his or her research protocols. This responsibility may be discharged either personally, if the PI is a physician or dentist with the requisite expertise, or by a physician co-investigator, fellow, or resident who possesses the requisite clinical expertise and admitting privileges. The qualifications and expertise of physicians or dentists who provide clinical care for research participants must meet institutional and applicable local guidelines and bylaws. GAC review of protocols must include a determination that medical coverage for research subjects will be optimal. Plans for emergency coverage by licensed M.D.s and, where appropriate, for night care, must be formalized for each protocol, or for the entire GCRC.

2. **Intercurrent Illnesses:** The appropriate disposition of a patient who develops an illness during the course of study depends on the severity of the illness and its relationship to the

research. The patient may be treated on the GCRC when the illness is unrelated to the research but is anticipated to be of short duration. If the intercurrent illness requires termination of the studies or their interruption for a substantial period, other arrangements for the patient's care should be made.

L. Data and Safety Monitoring Plans:

In 1998 and 2000, NIH issued policies on Data and Safety Monitoring for Clinical Trials. These policies, NIH Policy for Data and Safety Monitoring and Further Guidance on a Data Safety and Monitoring For Phase I and Phase II Trials, provide NIH requirements for data and safety monitoring of clinical trials supported by NIH funds.

In addition, NCRR requires that all GCRC protocols, not just clinical trials, must have a DSM plan that has been approved by the GAC. Based on an exemption from the Office of the Director of NIH, GAC-approved protocols do not require additional approval by NCRR staff. However, GAC approval does not supplant the required approval by staff at other NIH Institutes and Centers that support the research.

Further, NCRR requires that all protocols that place participants at significant risk must have an independent DSMB. The determination of significant risk is to be made by the local GAC. The charter (or list of the responsibilities, meeting frequency, etc.) and membership of any DSMB, as detailed in the NIH Guidances on Data and Safety Monitoring referenced above, must be included in the DSM plan of any protocol that includes a DSMB.

The GAC is to document in its minutes its approval of the DSM plans. Those minutes may be reviewed by NCRR or other NIH program staff who are responsible for oversight of specific clinical trials conducted on the GCRC. In addition, GCRC program staff or members of the site-visit team may request access to the log during the competitive renewal process of the GCRC.

M. Reporting Serious Adverse Events (SAEs):

Federal regulations (45 CFR Part 46, Subpart A, i.e., the "Common Rule"), which are applicable to all GCRC studies, require reporting of "unanticipated problems" involving risks to participants to the IRB, the appropriate institutional officials, and the Federal Department or Agency head. In addition, for those studies regulated by the FDA (21 CFR 312.32), sponsors must notify the FDA and participating investigators of any adverse event associated with the use of test article that is "both serious and unexpected." In addition, NIH has issued several policies and guidances related to adverse event reporting and serious adverse event reporting. These include:

NIH Policy for Data and Safety Monitoring;

Further Guidance on a Data Safety and Monitoring For Phase I and Phase II Trials;

Guidance on Reporting Adverse Events to Institutional Review Boards for NIH- Supported Multicenter Clinical Trials;

Notice to NIH Grantees/Contractors Regarding Letters or Notices from the Food and Drug Administration (FDA).

In addition, whenever a gene transfer protocol conducted on the GCRC results in a report to the FDA of a serious unexpected adverse event or a report to the IRB of an unanticipated problem involving risks to subjects or others, a copy of that report should be sent at the same time to: the Office of Biotechnology Activities, NIH; NCRR's DCRR; and the categorical NIH Institute (e.g., NCI, NIAID) supporting the study. In all such SAE reports to NIH, no names or other patient-identifiable material should be included.

N. Training and Career Development:

The training of health professionals in the methods of clinical investigation should be an integral part of the research effort of every GCRC. The GCRC should serve as the institutional focus for training in clinical research methodology, bioethics, biostatistics, clinical trial design, epidemiological studies, and basic laboratory methods. Formal courses may be set up for this goal and include National Research Service Award (NRSA) fellows and trainees, K12 and K23 awardees, and junior faculty.

Regular rotation on the GCRC by research fellows, house officers, and medical, nursing, and dietary students is encouraged. Because GCRCs are expected to represent models of excellence in current clinical research techniques, they also may be used for other instructional purposes, including programs of continuing education for practicing physicians, nurses, and dietitians. These activities, along with the use of the Core Laboratory for training in research methodology, are the responsibility of the PD, but they may be delegated to an Associate or Assistant PD.

Each student or postdoctoral fellow who participates in research on a GCRC must have a qualified mentor identified in GCRC records. This supervisor, typically the PI of the protocol on which the trainee is working, is responsible for the medical and scientific quality of the work performed by the trainee.

O. Annual Reports:

Each grantee institution is required to submit an Annual Report of scientific progress and an annual Financial Status Report (FSR) within 90 days after completion of the grant year. These reports are reviewed by NIH staff and are used for planning and evaluation. Through these reports, the NIH staff is kept apprised of current GCRC research activities and accomplishments for Congressional reports and budget justifications and for other reports.

P. Credit on Publications:

All publications that result from utilization of any of the GCRC resources (e.g., inpatient area, outpatient area, Core Laboratory, Informatics Core) should cite the grant as a contributing source of support and indicate the GCRC grant number, including the prefix "M01RR." Publications crediting the GCRC grant should be approved by all listed coauthors. Each GCRC must maintain a current and complete bibliography of publications that resulted from studies that used GCRC resources for inclusion in its Annual Report. It is recommended that GCRC scientific and administrative records be retained for at least five years.

Q. Industry-Sponsored Research:

GCRCs are sometimes used for projects funded in whole or in part by for-profit organizations. Investigator-initiated projects that are partially supported by such an organization through a grant of unrestricted funds or by a donation of drugs or devices may be pursued on the GCRC in the usual manner, subject to the usual IRB and GAC review and approval. Funds from the proprietary organization that are budgeted for research patient care must be credited to the patient care category of the GCRC grant if the GCRC is used. Copies of the agreement with the drug company or other source must be maintained in the GCRC's administrative files. In addition, copies of appropriate regulatory documents and other relevant correspondence are to be maintained in the GCRC's research project files. This includes, but is not limited to, all FDA-required documents and relative correspondence.

Those projects designed by for-profit organizations will be considered industry initiated. That organization is expected to pay for the use of the GCRC facilities at the same rates that it would pay for any other hospital beds and ancillary charges at that institution. This can be accomplished by classifying research subjects in such projects as Category D patients. (See Section IV-G.) All Category D patient charges are to be paid to the hospital from funds provided by the commercial organization. In some cases, investigators may add additional research aims to the project. In that case, the GAC ascertains the relative resource needs to be contributed by the company, GCRC, and investigator's resources. All industry-initiated projects must be approved for use of the GCRC by the GAC and include a DSM plan. Industry-initiated projects should constitute only a small portion of total GCRC activity. In some cases, a commercial organization may provide clinical research funds for an investigator-initiated study. If investigator-initiated, the research project is appropriately

classified as Category A or Category B rather than Category D. The funds provided by industry are to be credited to the patient-care category of the GCRC grant.

The determination of whether a research project is industry-initiated or investigator-initiated is to be made by the GAC, using the above general principles after reviewing the appropriate documents. Deliberations are to be documented in the minutes of the GAC meetings. Investigators who are receiving industry support for projects conducted on the GCRC must be free to publish or distribute data from such studies without restriction.

R. Clinical Research Feasibility Funds (CReFF) Program:

GCRC grant funds may be used to support pilot studies subject to review and approval by the GAC. A GCRC may rebudget unrestricted GCRC grant funds for this purpose.

A GCRC also may request additional funds for a CReFF program. In such a case, the GCRC must establish and submit to NCRR, guidelines for: eligibility; selection criteria for candidate investigators and projects; and a plan for evaluating success. Eligibility would be limited to junior faculty–ranks equal to or less than assistant professor–or senior faculty only if they have a change in research career path. Recipients will be required to prepare a final report. The CReFF awards could be up to $20,000 for one-year renewable projects; each GCRC would be limited to $100,000 annually. The CReFF program will be reviewed as part of the competitive renewal of the GCRC grant.

S. Availability of GCRC Resources for Long-Term Follow-Up of Participants in Gene Transfer Protocols: See NOT-RR-04-005.

III. PHYSICAL FACILITIES

A. General:

The design of a GCRC must facilitate the proper conduct of patient-oriented investigations. Usually, the GCRC is geographically discrete and adjacent to a routine hospital patient care area/unit. It should include adequate space that enables research operations to be performed in an optimal manner. While regular hospital traffic routes should not traverse the GCRC, the GCRC should be located close to other patient care areas if possible, so that clinical services and emergency care are readily available. The GCRC must be in a facility accredited by the JCAHO or certified to accept Medicare or Medicaid reimbursement. All renovations of GCRCs financed by NIH grant funds must meet applicable Federal guidelines (i.e., Guidelines for Construction and Equipment of Hospital and Medical Facilities).

GCRC relocation, within the current hospital or to a new hospital, or changes in the current

space that differ from those recommended in the last peer review, must be reviewed and approved by NCRR prior to initiating the modifications. Detailed floor plans including a list that indicates the use and square footage for each room, a narrative justification, and an estimate of cost for the revised GCRC site should be co-signed by either the PD or PI and the appropriate Business Official and submitted to NCRR. When such a proposed change in space would result in an increase in Routine Cost and/or Space Cost to be requested from NCRR in the future, NCRR may decide to not fund the increased Routine Cost or Space Cost unless the planned change in space and estimated attendant increase in Routine Cost and/or Space Cost was approved in advance by NCRR; this advance approval by NCRR is required independent of the source of funds paying for the renovation/relocation/expansion.

B. Inpatient Area:

Space requirements for the inpatient area are dependent on local codes, JCAHO standards, research needs, and Federal guidelines. Space should be adequate both for patient comfort and for equipment used in bedside studies. It is preferable that at least half of the research beds are located in private rooms to accommodate gender or age differences. Rooms that provide controlled environments such as those involving laminar air flow, special monitoring, or isolation, may be supported if justified scientifically for patient or staff safety. The nurses' station should be large enough to accommodate the nursing and paramedical staffs. Ideally, the office for Head Nurse/Nurse Manager, a doctors' writing area, and a patient lounge, which may also serve as a reception area for outpatient research studies, should be provided. A treatment or procedure room usually is essential for research and patient care procedures. Adequate storage space and utility rooms, in keeping with JCAHO guidelines, also must be provided. Occasionally, more than one inpatient facility may be required for a GCRC, such as when large numbers of both pediatric and adult patients are being seen simultaneously.

C. Outpatient Area:

A facility for outpatient research can be located either in the GCRC inpatient area or in a unit that is geographically separate from the hospital outpatient department. A contiguous unit could share supporting facilities and paramedical staffs with the inpatient GCRC and usually is more cost-effective and provides greater flexibility for research. Space requirements of the outpatient area depend upon the scope of the outpatient activities. The inpatient reception area, patient lounge, and examining rooms can be utilized if they are of sufficient size. In some cases, patient beds on discrete GCRCs may be used for complex outpatient studies that require a visit lasting several hours. Additional offices and treatment rooms may be necessary. The area should be functionally designed specifically for outpatient studies; a doctor's consultation room may serve two or more examining rooms.

Renovations for ambulatory research operations need not be extensive or costly. Many existing

GCRCs can handle outpatient visits with little modification of their physical structure. When the GCRC outpatient research must be carried out in a unit of the hospital outpatient department, efforts should be made to maintain the discrete nature of the outpatient research area with regard to both location and scheduling.

D. Core Laboratory:

Core Laboratory research facilities should be within the boundaries of the GCRC or in a nearby location. A specimen processing area is often an essential part of the GCRC, even when no analytical Core Laboratory is required.

E. Bionutrition Research Facility:

A Bionutrition Research area, if justified for the proposed research program, should be located on or near the GCRC. This may include a metabolic kitchen depending on the scope of bionutrition activities. An office for the Bionutrition Research Manager should be located on or near the GCRC.

F. Office and Conference Space:

Office space for the PD, the administrative staff, and the RSA should be provided on or near the GCRC. Offices for an Associate/Assistant PD, Core Laboratory Director, or other personnel are sometimes justified. A conference room often is needed for meetings, research seminars, and teaching purposes, especially for large GCRCs.

The Informatics Core should be located in dedicated space on or adjacent to the GCRC. The physical facilities should include an Informatics Core Manager's office, a user/training room, and a secured room for the file server(s). The computer facilities should be configured for both local and remote access. Both hardware and software should be the focus of a rational renewal strategy to maintain and upgrade information technologies that meet the evolving needs of the investigators.

IV. GRANT MANAGEMENT

A. General:

The award and administration of GCRC grant funds are subject to the laws, regulations, and policies indicated in the Notice of Grant Award (NOGA), the Terms and Conditions therein, and these Guidelines. Awarded funds for patient care costs may not be transferred to other budget categories without prior approval from both NCRR's DCRR and the OGM. Awarded funds for nursing and bionutrition salaries and their related fringe benefits may be rebudgeted to

other budget categories without NCRR prior approval in accordance with NIH rebudgeting policies. Rebudgeting between nonrestricted budget categories must be in compliance with NIH rebudgeting policies and, where significant, should be approved by the GAC. As described below, Category A activities may be commingled with other patient-oriented research activities (such as Categories B and D activities), provided appropriate program and resource utilization and cost accounting is maintained for each study. In addition, other patient-oriented research units may be colocated with a GCRC, provided appropriate fiscal accountability exists.

In accordance with NCRR policy, the recurring direct costs (direct costs excluding equipment and alterations and renovations) requested for the first year of a competitive renewal application cannot exceed the final noncompeting year's direct recurring costs budget by more than 20 percent. Where this policy may significantly limit the program scope of the proposed research, the applicant may request a waiver of the 20 percent ceiling. A letter, clearly justifying the request for a waiver, must be submitted to NCRR's DCRR, well in advance of the application receipt date. The waiver to the ceiling must be approved in writing by NCRR's DCRR, before the Center's competing renewal application is submitted and accepted.

B. Personnel Costs:

Salaries and wages of personnel may be charged to the grant in proportion to the time devoted to GCRC activities. Salaries of personnel paid by the GCRC grant must not exceed the salaries of personnel in comparable positions elsewhere within the institution. Fringe benefits, if not included as an F&A cost, are allowable as a direct cost in proportion to the salaries charged to the grant, provided that such payments are made under institutional policies that are formally established and consistently applied. Charges must be in accord with applicable institutional policies, and records must be maintained to substantiate these charges. Sabbatical leave salaries for GCRC personnel are not allowable charges to the GCRC grant; however, sabbatical leave costs to the institution may be included in a composite fringe benefit rate or in the institution's F&A cost rate. An appropriate salary may be charged to the GCRC grant for the person performing the duties of the GCRC staff member who is on sabbatical.

C. Equipment:

Fixed or movable equipment for patient, laboratory, dietary, informatics, and administrative areas may be purchased with grant funds if necessary for GCRC activities, provided that such equipment is not otherwise available to the GCRC from within the institution. Equipment not requested in initial, renewal, or supplemental applications may be purchased from unexpended grant funds, as permitted by institutional and *NIH Grants Policy Guidelines*. Requests for such purchases from funds available in patient-care categories, accompanied by a detailed justification, must be submitted to NCRR by the PD and co-signed by an authorized Business Official of the institution.

D. Consumable Supplies:

Consumable supplies for the Core Laboratory, Informatics Core, RSA, and the GCRC administrative office may be purchased with grant funds provided in the supply budget category. Routine hospital, drug, and raw food supplies ordinarily are provided for within the patient care cost budget categories and are not directly charged to the supply budget category of the grant.

E. Travel:

Domestic travel by the PD and other staff members, which will provide direct benefit to the administration of the GCRC, may be paid for by the grant. This may include meetings of the PDs, RSAs, Informatics Core Managers, Biostatisticians, Administrative Directors, Nurse Managers, and Research Bionutritionists, and travel of GCRC personnel for consultation with NCRR. These travel/meeting costs are specifically indicated on the NOGA. Funds for patient travel are allowable charges to a GCRC grant only under the conditions specified below under "Other."

F. Other:

The Other category usually encompasses miscellaneous services directly related to the GCRC operations, such as software and hardware maintenance and training, equipment maintenance contracts, and duplicating services. Publications such as patient handbooks, annual reports for the lay public, and public information documents, are allowable as publication costs and may be included in the Other category. However, research publication costs (page charges, reprints, etc.) are an individual investigator's expense and are not chargeable to the GCRC grant. Subscriptions to research publications are allowable only if they are of direct relevance to a significant number of GCRC staff members. Membership fees to scientific and professional organizations are not allowable charges to a GCRC grant.

Payments from the GCRC grant to research participants (including for travel) may be made when all three of the following conditions are met:

1. Research participants are compensated in amounts that are not coercive, as approved by the IRB;

2. The protocol, to be performed on the GCRC, is a GCRC-sponsored pilot project with no external funding; and

3. Payment from the GCRC grant and the amount of the payment are approved by the GAC.

In addition; payment for patient travel may be made when only conditions one and three above apply, with prior NCRR approval.

G. Patient-Care Costs:

l. General: Research patient-care costs incurred under GCRC grants by the grantee institution/hospital must be computed using research patient-care rates or amounts established by the appropriate Regional Office of the Division of Cost Allocation of the Department of Health and Human Services (DCA, DHHS). Such rates must be used by the grantee institution/hospital in all requests and claims for reimbursement for research patient-care costs. The grantee institution/hospital must submit patient-care rate proposals annually to the DCA, DHHS Regional Office and reply promptly to inquiries from that Office. If a hospital incurring research patient-care costs under a GCRC grant is a consortium participant and not the grantee institution/hospital, then the grantee institution/hospital will be responsible for establishing with the consortium hospital an appropriate rate or amount that will be reimbursed for such costs. However, if the consortium hospital has an established research patient-care rate agreement with DHHS, then the DHHS rate must be used for calculation and reimbursement of research patient-care costs.

Inpatient utilization is based on midnight census. If a patient's participation in an approved protocol exceeds 24 hours but does not entail presence on the unit at midnight of the following day, the utilization may be recorded as a single inpatient day plus a single outpatient visit of the appropriate category.

2. Patient Categories: Each patient admitted to the GCRC shall be assigned to one of four categories: Research (Category A), Research Service (Category B), Industry-Initiated (Category D), and Non-Research (Category C). These assignments are to be made prospectively for each research project by the PD and GAC, in consultation with the involved investigator. The GAC evaluation of research projects for GCRC use is to be made exclusively on the basis of the scientific merit of the projects and their need for the GCRC, without regard to the assignment of patients to Category A or B. In all cases, NIH-funded clinical research has the highest priority status.

GCRC grant funds pay for research costs. They are not used to pay for established patient medical care or treatment during the course of research. When Category C and Category D patients are admitted to a GCRC, all costs for their care are charged to the patients or third parties rather than to the grant.

a. <u>Research Patients (Category A)</u>: These are research inpatient days or outpatient visits utilized solely for research purposes. All hospitalization costs associated with Category A research days or visits are the financial responsibility of the institution

through the GCRC grant or the investigator's research grant. Persons who are hospitalized for research purposes only, but whose care is partly supported by non-GCRC funds, (e.g., other grants, industry, the Centers for Medicare & Medicaid Services under its Clinical Trials Final National Coverage Decision) also may be classified as Category A. This category includes normal volunteers or control subjects and patients who may participate in research projects that include unproven forms of therapy or diagnostic techniques that may subsequently become standards of medical therapy or diagnosis. Even though a patient may have a third party carrier and have an underlying disease, the GCRC assumes all research costs related to patients in this category.

GCRC grant funds may be used to pay all costs, thereby encompassing the usual care costs, which are part of the research project, as well as research care costs. This financial responsibility is assumed for the entire period of hospitalization or outpatient visit, research testing, or provided services for patients who would not otherwise have been hospitalized or received such tests or services except for their participation in the research study. Any exceptions should be documented in GCRC administrative records.

These patients may include persons to whom no health advantages may be expected to accrue as a result of the hospitalization or outpatient visit. Examples would be persons with genetic or other abnormalities of interest to the investigator, and those persons who, although sick, would not have been brought to the hospital except for the research studies.

b. Research Service Patients (Category B): This category pertains to patients who require hospitalization or outpatient studies for diagnosis or treatment according to established standards of care. Although these patients also participate in GCRC-based research studies, the cost of established medical care (i.e., non-research care for Category B patients) is not charged to the grant. The patient or third party carrier is responsible for those costs. The institution is responsible for all billings and collections on these patients. A patient care credit, or offset, for each Category B inpatient day or outpatient visit is credited to the patient care category of the grant based on the patient-care rate agreement for inpatient days or the rate developed by the GAC for outpatient visits. (See Section IV-G-6.) The cost of those ancillary services performed solely for research on Category B patients and not related to their routine medical care should be charged to the grant and not appear on the patient's hospital bill that is submitted to either the patient or the insurance carrier. Patients who meet the Category B classification criteria may not be classified as Category A simply because they lack applicable insurance.

c. **Industry-Initiated Projects (Category D):** This category includes inpatient days or outpatient visits utilized for an industry-initiated study. All charges are paid by industry. For each Category D inpatient day, a credit is provided to the patient care category of the grant based on the patient care rate agreement. In addition, the GCRC receives a credit for each outpatient visit and use of any other GCRC resources. The charge for each project is to be developed by the GAC and credited to the patient care category of the GCRC grant. (See Section IV-G-6.)

d. **Non-Research Patients (Category C):** Patients who are not participating in a research project may be admitted to the GCRC solely for the purpose of diagnosis or treatment according to established procedures, only when there is space and staffing available on the GCRC. The purpose of Category C inpatient admissions and outpatient visits is to decrease the cost of the operation of a discrete GCRC. As with Category B patients, the hospital is responsible for all billings and collections that involve Category C patients. Because Category C patients are not participating in research projects, no charges for their hospitalization or visits may be made to the grant. The requirements for providing credits to the grant are the same for Category C patients as for Categories B and D patients.

It is essential that the presence of Categories D and C patients not compromise other research activities involving Categories A and B patients on the GCRC. Admission of all Category C patients must, therefore, be at the discretion of the PD and the GAC. Dialysis patients, post-operative patients, intensive-care patients, and other patients who require an extraordinary level of paramedical and nursing effort should not be admitted as Category C patients.

3. Scatter-bed Inpatient Days:

a. Category A:

i. The cost of occasional, unexpected, temporary use of special facilities, such as an intensive care unit or other off-site area uniquely required to accommodate a research patient, may be charged to the GCRC grant provided that the care is required by the nature of the clinical research or by an illness resulting from the research; the care is provided in a specialized area (intensive care unit, coronary care unit, etc.); the occasional patient remains on the GCRC census under the scatter-bed classification while in the special care unit; and there is no duplication of payment for patient care. The GAC must review and approve this local activity.

ii. If the use of special facilities such as an intensive care unit or other off-site area is to be an established part of a GCRC research project and was not previously peer reviewed, prior written approval from NCRR is required. The request is to be co-

signed by the appropriate Business Official.

iii. If the cost of the proposed scatter-bed research activity combined with the support of the original peer-reviewed and recommended configuration of a GCRC exceeds the National Advisory Research Resources Council (NARRC)-recommended funding level, then a competitive supplement may be submitted for peer review of the request.

b. **Category B:** As defined above for Category B inpatients on the unit, Category B scatter-bed patients require hospitalization for diagnosis or treatment according to established standards of care but are also research subjects. These off-site inpatients may require ancillary services solely for research purposes that may be charged to the grant. Scatter-bed B research inpatients with ancillary costs charged to the GCRC grant will be tracked as scatter-bed B days. If a GCRC research nurse is required, the nurse's time is tracked separately as "Scatter-bed Research Nurse Hours." (See below.)

c. **Category C and Category D:** These categories are not classifications used for scatter-bed research days.

4. Scatter-bed Research Nurse Hours:

a. **Category A and Category B:** A GCRC research nurse may be required to perform the research component of a study on a Category B inpatient hospitalized off site on an approved scatter-bed research project. Scatter-bed research nurse hours will be tracked by project for nurses who are paid directly by the GCRC grant. The hours tracked will reflect all the requisite time associated for each research project (e.g., scheduling, preparation, direct patient research procedures, chart entry). Scatter-bed research nurse hours are entered in the Annual Report for each subproject by patient category (A, B, or D). The scatter-bed research nurse hours associated with all off-site research inpatients should be recorded. If ancillary costs are not charged to the GCRC grant, no Category B scatter-bed inpatient days are recorded. Off-site "B" research inpatient projects that have no ancillary charges will require only scatter-bed nurse hours to be tracked. Category A scatter-bed days are recorded, since either inpatient costs or ancillary costs (or both) are paid by the GCRC grant. Scatter-bed research nurse hours for Category A projects will count only the hours of nurses paid directly by the GCRC grant, not those nurses whose salaries are included in a *per diem* charge.

b. **Category D:** With the approval of the GAC, a Category D project with patients hospitalized off site may have a scatter-bed research nurse assist in the study. Scatter-bed research nurse time for an off-site Category D research project should be

tracked and appropriate financial credit should be made to the GCRC grant.

c. All scatter-bed research nurse activity must take place in a facility either accredited by JCAHO or certified to accept Medicare and/or Medicaid reimbursement.

5. **Outpatient and Research Meal Visits:** A GCRC research subject who is not hospitalized at midnight is considered to be an outpatient. Thus, an outpatient visit could be as short as a few minutes or as long as almost 24 hours. The visit may take place on the GCRC unit or at a remote site, as long as it is funded by the GCRC grant and/or involves a GCRC nurse. There is no category called "scatter outpatient visit."

   When a research subject is on the unit to eat or pick up a research meal and has no contact with either GCRC nurses or investigators, the interaction is categorized as a research meal visit, not as an outpatient visit. The research meal visits should be tracked and reported in the Nutrition section of the Administrative Narratives in the Annual Progress Report (APR) and listed as "research meal visits." If a research subject comes to the GCRC for more than eating or picking up a research meal (such as contact with a bionutritionist for a diet history or diet instruction or a procedure such as anthropometric measurements), then it may be counted in the census as an outpatient visit.

6. **Outpatient Visit Credits:** Charges for Category D (industry-initiated) visits, Category C visits, and the non-research portion of Category B visits are to be credited to the GCRC grant. This activity must be reflected in the computations on the census page of the APR, and it must be included as a credit in the patient care computation pages of the APR.

   For each project, an appropriate credit, preferably based on an hourly rate, must be computed. When developing a rate, include all utilized components of the GCRC (i.e., program directorship, administration, RSA, research bionutrition, nursing, core laboratory, computer, biostatistical services, space charges, as well as any other appropriate GCRC resource). A rate should be established and approved by the GAC.

7. **Changes in Patient Category:** A patient's category may change during the hospital stay on the GCRC. For example, a patient may be designated as Category B during the first part of an admission, when the patient would have been hospitalized regardless of research participation, and subsequently as Category A after the completion of standard care because components of the research project have yet to be completed. Similarly, part of a research subject's hospital stay may be Category D and another portion Category A or B. The categorization is determined prospectively by the GAC.

8. **GCRC Funding Methods:** There are two general means for funding of GCRCs: the Discrete Method and the Per Diem Method. The method chosen depends on

cost-effectiveness, unit size, and institutional constraints, and is determined by negotiations between the grantee institution and NCRR staff.

a. **Discrete Unit Method:** With this method, most often used for large GCRCs, the expected cost of all research inpatient days, nursing, dietary services, and other fixed expenses are funded in the grant award. When Research Service (Category B), Industry-Initiated (Category D), or Non-Research (Category C) inpatients are cared for on the GCRC, the grant is reimbursed by the hospital by means of a credit ("offset") to the grant based on the annual DHHS-negotiated rate agreement. Category B, C and D patient credits may not be rebudgeted to nonrestricted budget categories by the grantee institution without prior approval from NCRR staff.

b. **Per Diem Method:** With this method, the expected cost of the Research Patient (Category A) inpatient days is provided in the grant award, but the hospital is reimbursed only for the Category A days actually used. The payment for each day is based on an average routine per diem rate for Category A patients, adjusted for any items funded directly by the grant, such as some or all of the nursing.

c. **Discrete vs. Per Diem Comparison:** In comparing per diem versus discrete methods of funding, the following should be used as a guide:

	Discrete	**Per Diem**
Space Cost	N/A	
Per Diem Cost	N/A	
Routine Costs		N/A
Nursing Salaries (FTEs)		
Bionutrition Salaries (FTEs)		
Service Patient Credits		N/A

Description of Cost Items:

Space Costs – On a per diem GCRC, space costs may be requested for administrative offices, laboratory space, computer space, and research bionutrition space. A detailed description of square feet per office/room should be provided. Cost should be calculated as the number of square feet applicable to these areas, multiplied by the square-foot dollar rate for the hospital.

Per Diem – The per diem cost is usually the Medicare rate for the hospital. This rate for a per diem Center should be the Service Patient Credit rate for a discrete Center. The per diem is calculated by applying this rate to the number of Category A days requested.

Routine Costs – This is the cost for the total inpatient space of the GCRC.

Nursing – On a per diem GCRC, salaries for a Nurse Manager and specialized clinical research nurses may be paid from the GCRC grant. The number of nurses depends on the level of activity and the intensity of nursing care required.

Bionutrition Research Salaries – On a per diem GCRC, the dietary component must be justified based on the need for a bionutrition research component. Normal patient meals should be provided by the central hospital kitchen.

Service Patient Credits – This is the Medicare rate applied to B, C, and D patients on a discrete Center.

Ancillary costs are generally not affected by the method of funding, and thus are not considered in the above.

9. **Scatter-bed Reimbursement:** Some studies require that patients be cared for in beds not located on the GCRC. These are referred to as scatter-beds. If Category A scatter-bed days have been funded in the award statement, or prior approval has been obtained from NCRR, patient-care costs will be provided using a negotiated inpatient routine per diem applicable to the area where the patient is housed. Scatter-bed patients often are Category B, in which case the only cost to the grant is for the ancillary costs associated with the research.

10. **Ancillaries:** All ancillary services provided to Category A patients and those provided to Category B patients that are not required for their routine medical care but are performed solely for research can be supported from GCRC grant funds. Ancillary services are defined as services routinely available through hospital departments for all patients in the hospital. This definition applies even when these services are purchased from sources outside the hospital for reasons of economy or efficiency. Tests needed by individual investigators for their research are not proper charges to the GCRC grant if the tests are not routinely available to all patients in the hospital. Also, services provided either by the laboratory of a GCRC researcher or by a hospital laboratory or service that is directed by a GCRC researcher (even if that researcher has a contractual arrangement with the hospital to provide these services) may not be charged to the GCRC grant for any project for which that researcher is the PI or a collaborator. Research ancillary charges must be reduced to cost (discounted according to the Medicare or GCRC rate), based upon the Negotiated

Rate Agreement between the hospital and DHHS.

11. **Program Income:** Program income is defined as the gross income earned by a grant recipient that is generated directly by an activity supported by the grant or earned as a result of the grant. (See 45 CFR 74.2 and 74.24 for additional information.) An example of program income is fees resulting from charges made for laboratory tests performed by the GCRC Core Laboratory. An estimate of the amount and source of program income expected to be generated as a result of the GCRC grant award must be included on the Checklist Page of all competing and noncompeting continuation applications. Net program income earned during a budget period must be reported on the long form FSR (except for program income earned as a result of inventions, to which special rules apply). Costs incident to the generation of program income may be deducted from gross income to determine program income, provided these costs have not been charged to the award.

    Program Income earned during the project period shall be retained by the GCRC recipient and, in accordance with the terms and conditions of the award, used in the following way:

    a. The first $25,000 earned during a budget period is added to funds committed to the project or program and used to further the objectives of eligible projects or program;

    b. Any amount over $25,000 earned during a budget period is to be deducted from the total project or program allowable costs in determining the net allowable costs on which the Federal share of costs is based. NCRR may offset a future award by this amount or reauthorize it for expenditure on a future award.

12. **Off-Site Research Visits (non-JCAHO):** As stated on the first page of these GCRC Guidelines, "Inpatient and outpatient areas of the GCRC must be located in facilities either accredited by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) or certified to accept Medicare and/or Medicaid reimbursement." Accordingly, any inpatient day or outpatient visit reported in the GCRC census must take place in such an accredited or certified facility.

    The GCRC Guidelines were modified (effective April 1, 2003) to allow low-risk research activity (e.g., administering a questionnaire, buccal swab) by GCRC grant-supported personnel (e.g., nurses) to take place in facilities that are neither JCAHO-accredited nor Medicare- or Medicaid-certified (e.g., school, church, home, museum). Such activity is to be reported in the GCRC census, not as inpatient days or outpatient visits, but rather as a new category called "off-site research visits" (ORVs). The following caveats apply to any GCRC research activity that takes place off site:

        1. Although all GCRC protocols continue to require approval of the IRB and GAC

before they may be initiated, and a DSM plan, the GAC review of protocols involving ORVs must include (and document in the minutes) an assessment that the facility in which the ORV is to be conducted will not compromise research subject safety or data confidentiality, and that the medical coverage will be appropriate for the risk level of the proposed research activity.

2. As with all GCRC protocols, the protocol should not be coercive and investigators should exercise appropriate sensitivity regarding the populations to be studied.

3. Only category A and B ORVs are allowed. GCRC personnel are not allowed to participate in category C or D activity in non-accredited facilities.

4. Currently, ORVs are allowed only when they are part of a study receiving NIH or comparable peer-reviewed support other than the GCRC (M01) grant.

13. GCRC Modified Classification for Rare Disease Research: Advances in the treatment of rare diseases are not sufficiently likely to be commercially viable to attract industry-supported development. This is acknowledged by the Orphan Drug Act that specifically permits the Secretary of the DHHS to make grants and/or contracts to assist in defraying the costs of qualified clinical testing of drugs, devices, or foods for rare diseases and conditions.

The GCRC Program, following this lead, modified the GCRC research category classification to facilitate testing of new agents for patients with rare diseases. Consequently, clinical trials of drugs and other candidate therapies or interventions for rare diseases may be classified by the local GAC as category A, instead of D, for industry-initiated protocols as described below. (All investigator-initiated trials, designed by a single investigator or a consortium of investigators, are already classified as category A.)

The protocol must be for a rare disease. Rare disease refers to "any disease or condition that either (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug or other therapeutic agent." A broad group of appropriate experts, including some from outside the institution, must review and find the protocol meritorious prior to its presentation to the GAC. The protocol must conform to the format and policies required by the GAC.

H. Professional Fees:

1. **Category A patients:** Physicians' fees or other professional services may not be charged

to the grant for Category A patients, except when included in the charge for a hospital service to a research patient AND that hospital department providing the service, such as radiology, pathology, or anesthesiology has a contractual agreement with the grantee institution or participating hospital. Administrative approval by NCRR is required prior to implementing payment for those professional fees.

2. **Category B patients:** Physicians' fees may not be charged to the GCRC grant for Category B patients. However, physicians' fees may be charged directly to Category B patients or third parties. Budgetary records should be maintained to document this process. Real or apparent conflicts of interest must be avoided. Professional fees charged and collected by the hospital on behalf of GCRC investigators should be deposited directly into divisional or departmental accounts so that no investigator is the direct recipient of patient fees.

I. Consultant Fees:

Consultant fees to physicians are not allowable charges to a GCRC grant.

J. Alterations and Renovations:

Approved renovations of an existing structure to provide facilities for a GCRC may be paid by the grant. (See Physical Facilities Section.) Funds may not be used for new construction or for completion of "shell space." All renovations of GCRCs financed by NIH grants must meet applicable Federal guidelines (i.e., *Guidelines for Construction and Equipment of Hospital and Medical Facilities*, latest edition).

K. Facilities and Administrative Costs:

A special or off-campus F&A cost ("modified F&A") rate is normally required for all GCRC grants, since F&A costs such as depreciation, operations and maintenance, housekeeping, and space costs for the GCRC facilities are included in the direct component of patient care costs. Patient care costs also include F&A costs related to hospital-affiliated employees supported as a direct cost by the grant, regardless of the identity of the employer. Therefore, the base used to claim F&A cost must exclude all hospital-affiliated costs (salaries and fringe benefits for nurses, bionutritionists, ward clerks, social worker, etc., and patient care costs).

L. Overall GCRC Funding:

Funding for each GCRC each year is based on prior utilization and productivity and projected total (not just inpatient) patient-oriented research activity. This includes inpatient, scatter-bed, outpatient, nursing, research bionutrition, core laboratory, training, biostatistics, and computer analysis needs.

National Center for Research Resources
National Institutes of Health
Department of Health and Human Services

Division for Clinical Research Resources

Guidelines for the General Clinical Research Centers Program (M01)

Supplement I: Instructions for Preparing a GCRC (M01) Application

April 2005

An Administrative Document Issued by the
National Center for Research Resources (NCRR)

Contact Information:

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Division for Clinical Research Resources

INSTRUCTIONS FOR PREPARING A GCRC APPLICATION

I. ELIGIBILITY FOR GRANT SUPPORT

Medical institutions and hospitals are eligible for GCRC Program support. The primary purpose of a GCRC is to provide the clinical research infrastructure to investigators who receive their primary research funding from the other components of NIH. While most grantee institutions of the GCRC Program are affiliated with medical schools, other institutions devoted to medical research may also apply. Inpatient and outpatient areas of a GCRC must be located in a facility accredited by the JCAHO, or certified to accept Medicare and/or Medicaid reimbursement. GCRCs provide the infrastructure for high-quality clinical research for physician-scientists currently funded by Federal agencies, private foundations, and other peer-reviewed sources. The resources of a GCRC may include inpatient and outpatient facilities, specialized personnel, Core Laboratories, and other Core facilities.

II. SUBMISSION AND REVIEW OF APPLICATIONS

As GCRC applications exceed $500,000 in direct costs per year, permission must be obtained from NCRR prior to submission of an application. Investigators interested in submitting a new, renewal, or amended application should consult with DCRR staff long before the proposed submission date. If approved for submission, one of the submission dates listed below will be designated for acceptance of application.

Each new or competing GCRC application submitted to NIH is evaluated by three groups–first, by a site-visit team composed of members of the Clinical Research Review Committee and *ad hoc* consultants; next, by the Clinical Research Review Committee (Initial Review Group) of NCRR; and finally, by the NARRC, which makes its recommendations to the Director of NCRR. Criteria for evaluation of a new or competing renewal GCRC application include scientific merit of the proposed research, peer-reviewed research project support for GCRC investigators, program relevance, value as an institutional and regional resource, utilization by several medical disciplines, evidence of collaboration between basic and clinical scientists, availability of a sufficient research patient population, compliance with Federal regulations that relate to human subjects research, and the prospects for use of the GCRC as a clinical research training facility.

New, competing continuation (renewal), and competing supplemental applications, using Form PHS 398, are accepted and reviewed according to the following schedule:

Received By	Project Site Visit	CRR Committee Review	Council Review	Earliest Possible Funding Date
October 1	Nov. - Jan.	February	May	July 1
February 1	March - May	June	September	December 1
June 1	July-Sep.	October	January	April 1

Form PHS 398 is available at: http://grants.nih.gov/grants/forms.htm.

In accordance with NCRR policy, the recurring direct costs (direct costs excluding equipment and alteration and renovation) requested for the first-year budget of a competitive renewal application cannot exceed the most recently funded noncompeting year's direct recurring costs budget by more than 20 percent. When this policy may significantly limit the program scope of the proposed research, the applicant may request a waiver of the 20 percent ceiling. A letter, clearly justifying the request for a waiver, must be submitted to NCRR well in advance of the application receipt date cosigned by an authorized institutional business official and the PI. The waiver must be approved in writing by the DCRR before the Center's competing renewal application is submitted and accepted.

Applications are recommended by the NARRC for project periods of varying length, up to a maximum of five years. Funding of recommended initial or renewal applications depends on the availability of funds to NCRR, as well as the outcome of peer review.

Requests for support above the level previously recommended by the NARRC should be made by a competing supplemental (Type 3) grant application, using Form PHS 398. Competing supplemental requests will not be accepted without prior (at least six weeks prior to the anticipated submission) consultation with and approval by the DCRR. The format and review of supplemental grant applications are similar to those of new and renewal GCRC grant applications, except that the information to be included (projects, biographical sketches, tables, etc.) need be only the material required to justify support of the items requested in the supplemental application. The deadline receipt dates for supplemental applications are the same as those for new and renewal GCRC applications. Site visits are not usually required for supplemental applications, unless they are very large or require additional assessment of GCRC resources.

Competing supplemental applications dealing only with research on AIDS may receive an expedited review. Such applications should meet the criteria given in the previous paragraph with the following modifications: 1.) To be considered for expedited review, the submission dates are January 2, May 1, and September 1; and 2.) All projects in the supplemental application must be AIDS related. If a site visit is needed, expedited review may not be possible. PDs must consult with NCRR and receive approval before submitting such an AIDS competing supplemental application.

SUGGESTED STEPS IN PLANNING A GCRC APPLICATION

A. Examine the Guidelines for the GCRCs.

B. Discuss the need for a GCRC with investigators from different departments at your institution. From these discussions and from meetings with institutional administrators, determine the following:

1. A sufficient number of investigators with peer-reviewed sources of support will utilize the GCRC for clinical research;

2. The use of GCRC resources will be multidisciplinary;

3. Number and category of research inpatient days and outpatient visits required by the research projects;

4. Plans for implementation of an RSA program;

5. Biostatistical, Informatics Core, Core Laboratory, bionutrition, and administrative support is justified for the proposed research;

6. Optimal location for the GCRC within the institution; and

7. Institutional support.

C. Plan a visit to one or more established GCRCs to learn about GCRC administration and scientific oversight.

D. Make a preliminary sketch of the proposed GCRC. If necessary, obtain cost estimates for alterations and renovations.

E. Determine whether the hospital is JCAHO-approved and has a currently effective DHHS-negotiated hospitalization rate agreement for inpatients; if not, determine the basis to be used for calculating patient care costs.

F. Outline a draft proposal, and discuss it with DCRR staff.

III. SPECIFIC APPLICATION INSTRUCTIONS

Form PHS 398 must be used for all new and competing GCRC applications and supplemental applications. The specific instructions in these GCRC Guidelines are in addition to the

instructions of Form PHS 398. Follow Form PHS 398 instructions except where they differ from the specific instructions below.

Page limitations specified in Form PHS 398 instructions do not apply to GCRC applications; they have been modified as described below.

Submit a signed, original, typewritten application with the Checklist, and two single-sided, unbound, signed photocopies in one package to: Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 1040, Bethesda, MD 20892-7710 or for express/courier service use Bethesda, MD 20817-7710. In addition, send three single-sided copies to: Deputy Director, Office of Review, National Center for Research Resources, 6701 Democracy Boulevard, Room 1001, Bethesda, MD 20892-4874; or for express/courier service use Bethesda, MD 20817. Hand-delivered applications will not be accepted.

When submitting an amended (-A1) application, summarize in an "Introduction" section the substantial additions, deletions, and changes that have been made in all sections including all projects. Highlight these changes within the text of the "Research Plan" section by appropriate bracketing, indenting, or changing of typography. Do not underline or shade changes. Include any work done since the previous version was submitted. A revised application will be returned if it does not address criticisms in the previous summary statement and/or an "Introduction" is not included and/or substantial revisions are not clearly apparent.

Amended (-A1) applications may be reviewed at a site visit at the applicant institution, or may be reviewed at an "applicant interview," also called a "reverse site visit," or by another mechanism. NCRR's Office of Review (OR) will make that decision and will notify the applicant institution. Amended (-A2) applications generally will not be reviewed at a site visit. The Revised NIH Policy on Submission of a Revised (Amended) Application states that NIH will not consider any -A3 or higher amendment.

All applications are due on or before the established deadline date. No request for a waiver will be considered prior to receipt of the application, and there is no guarantee that the waiver will be granted by the Center for Scientific Review (CSR). NCRR staff cannot grant a waiver. To request a waiver, include an explanatory letter with the signed, completed application.

Do not send any supplementary or corrective material pertinent to an application after the receipt date without specific solicitation and agreement by the Scientific Review Administrator (SRA) of the Clinical Research Review Committee or the site-visit SRA. The reviewers are under no obligations to consider late material.

Pay close attention to type size specifications and limitations in the Form PHS 398 instructions.

Page 1
(Form PHS 398)

ITEM 1. TITLE OF PROJECT: General Clinical Research Center

ITEM 2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION: No

ITEM 3. a. NAME OF PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: Name of PI. Only the PI's name, and not the PD's name, should be entered on this line. If PD's name is entered here, the review of the application may be unduly delayed. Only one name per application is recognized in the NIH system.

ITEM 3. b, c, d, e, f, g. See instructions for Form PHS 398.

ITEM 4. HUMAN SUBJECTS RESEARCH: Yes

ITEM 5. VERTEBRATE ANIMALS: See instructions for Form PHS 398.

ITEM 6. DATES OF PROPOSED PERIOD OF SUPPORT

The entire proposed project period may not exceed five years. Applications cannot be funded until the NARRC has completed its review. The project period end date of supplemental applications may not extend beyond the funded project period end date of the Center grant. Refer to the most recent NOGA.

ITEM 7 through 15. See instructions for Form PHS 398.

Page 2
(Form PHS 398)

DESCRIPTION: Describe the major areas of investigation to be undertaken on the GCRC.

PERFORMANCE SITE(S): See instructions for Form PHS 398.

KEY PERSONNEL

Include only the PI, PD(s), Principal RSA, and other professionals (e.g., biostatistician, core laboratory director) for whom salary is requested. Do not include the names of the investigators of the individual projects.

TABLE OF CONTENTS

Structure the table of contents and the application according to the format below. Number pages consecutively from the beginning to the end of the application, without ancillary numbering systems. Applications which do not conform to this format may be returned.

PART I. BUDGET

A. Detailed Budget for Initial Budget Period (12 months or less)
B. Budget for Entire Proposed Project Period (up to 5 years)
C. Budgets Pertaining to Consortium/Contractual Arrangements and Budget Justification

PART II. BIOGRAPHICAL SKETCHES: Biographical sketches are to be in the PHS 398 Form format with no more than four pages per individual, including Research Support. Provide an alphabetized list of names with their page numbers.

PART III. RESOURCES AND ENVIRONMENT

A. Background and Introductory Statement
B. Organizational Framework
C. Administration
D. Patient Care
E. Training and Career Development
F. Core Laboratories
G. Biostatistical Support
H. Informatics Core
I. Physical Resources and Utilization
J. Other Existing or Planned Resources for Clinical Research
K. Data and Safety Monitoring Plan
L. Clinical Research Feasibility Funds
M. Data Sharing Plan
N. Research Subject Advocate

PART IV. RESEARCH PLAN

A. Accomplishments
B. Center Bibliography (for competing renewal applications)
C. Research Projects: listed by project PI in alphabetical order. Provide a page index for all

research projects at the beginning of Section IV-C, along with the title of the proposal and the name of protocol PI. Also indicate (Yes or No) whether the protocol has already been approved by the IRB and whether it has (Yes or No or Conditional) already been approved by the GAC.

PART V. TABLES

A. Faculty Member Research Participation
B. Training
C. Utilization of the Center, Last Three Years (for competing renewal applications)
D. Principal Users of the Center, Last Three Years (for competing renewal applications)
E. Proposed Scientific Agenda for the Site Visit and Abstract Package

PART VI. SITE-VISIT INFORMATION

Pages 4+5
(Form PHS 398)

PART I. BUDGET

A. Detailed Budget for the Initial Budget Period: For all new and competing continuation applications, the first budget period should be 12 months. For competing supplemental applications, the first budget period may be shorter than 12 months; consult with NCRR staff.

Itemize specific needs for the first budget period as follows:

1. Personnel: Follow carefully the Form PHS 398 instructions. In the justification, briefly describe the function of each position, and whether support is requested. List the holder of each position by name if the position is filled, and indicate whether he or she is employed by the university or hospital. All salaries requested must be consistent with institutional standards, applied regardless of the source of funds. If any support is requested for an employee of the Department of Veterans Affairs (VA), see the NIH Guide for Grants and Contracts, Vol. 18, No. 27, August 11, 1989.

For nursing and research bionutrition personnel requested, indicate the shift coverage the nursing and research bionutrition staffs will provide. Describe any unusual nursing and research bionutrition duties such as staffing for extended outpatient studies. If research bionutrition staffing is proposed, provide the following table:

Meals	% Current*	% Proposed
Planned, calculated, or modified		
Prepared or cooked		
Served		

* renewal applications only

2. Equipment: List separately each requested item of fixed and movable equipment costing more than $5,000. Provide a separate narrative justification for each equipment item requested, and indicate the investigators and projects that require the equipment.

3, 4, 5, 6. Supplies, Travel, Alterations and Renovations, and Other Expenses: See Guidelines for the GCRC Program for details on which items may be requested. Funds requested for the CreFF program should be requested under "Other."

7. Patient Care Costs: The patient care costs requested in the application for inpatients and outpatients should be supported by computations provided within the following pages.

   In Schedules 1-8, include each research project proposed for use of the GCRC that is expected to be active in the first year of the grant, if funded, including projects already underway at the time of the application. List them by project PI, in alphabetical order. Exclude projects that will be completed by the first year of the grant. All projects should be included, even if they are awaiting approval by the GAC or the IRB at the time of submission of the application. Indicate in the page index at the beginning of this section those projects not yet approved at the time the application is submitted.

   The number of category A days requested in item 6 on the following Patient Care Computation should match the total number of category A days in Schedule 1. The total ancillary costs requested in Item 6 on the following Patient Care Computation should match the total ancillary costs requested (hospital plus outside) in Schedule 1. The number of category A visits and ancillary costs requested in item 10 on the Patient Care Computation should match the total number of category A visits and ancillary costs in Schedule 5. This also applies to the numbers for category B days and visits, etc.

PATIENT CARE COMPUTATION: (Figures to be rounded to the nearest dollar)

INPATIENT

RATE USED

1. If proposed rate is used, show date filed with DHHS:
   MO _____ DAY _____ YEAR _____

2. If rate has been published by DHHS, show date of agreement:
   MO _____ DAY _____ YEAR _____

3. Show 12-month period of rate: _____ through _____

---

4. A. Routine Cost (or Space Cost for per diem method, if applicable): $_____
   B. Per Diem Method:
   __*__ Category A days x $_____ = $_____
   C. Scatter Beds:
   __*__ Category A days x $_____ = $_____

   Total (4A and 4C or 4B and 4C) $_____

---

5. Service Patient Credit (routine method)
   __*__ Category B days x $_____ = $_____
   __*__ Category C days x $_____ = $_____
   __*__ Category D days x $_____ = $_____
   All Other Inpatient Credits
   (Specify: grants, contracts, industry, etc.) $_____

   Total Credits ($_____)

---

6. Inpatient Ancillaries Required Solely for Research Purposes, Adjusted to Cost (Schedule 1)
   __*__ Category A days x $_____ = $_____
   __*__ Category B days x $_____ = $_____

   Scatter Beds:
   __*__ Category A days x $_____ = $_____
   __*__ Category B days x $_____ = $_____

   Total Inpatient Ancillaries $_____

---

7. Other Costs (Specify: drugs, raw food, special diets, outside laboratories, etc. Provide justification.) $_____

---

8. TOTAL INPATIENT REQUEST (Boxes 4, 6, and 7, less box 5) $_____

OUTPATIENT

9. Space Charge (If not included with inpatient routine costs) $_____

---

10. Outpatient Ancillaries Required Solely for Research Purposes, Adjusted to Cost (Schedule 2)

__*__ Category A visits x $_____ = $_____
__*__ Category B visits x $_____ = $_____

Total Outpatient Ancillaries $_____

---

11. Other Costs (Specify: drugs, raw food, special diets, outside laboratories, etc. Provide justification.) $_____

---

12. Credits

__*__ Category B visits x $_____ = $_____
__*__ Category C visits x $_____ = $_____
__*__ Category D visits x $_____ = $_____

All Other Inpatient Credits (Specify: grants, contracts, industry, etc.) $_____

Total Credits ($_____)

---

13. TOTAL OUTPATIENT REQUEST (Lines 9, 10, and 11, less line 12) $_____

TOTAL PATIENT CARE REQUEST (Lines 8 and 13) $_____

---

* list total annual projected number of days and visits in each category including those which require no ancillaries

Schedule 1 Category A Inpatient Projects*

Investigator Name	SPID Number	Project Title	Number of Days Per Year	Annual Cost** For Tests: Hospital Ancillaries	Annual Cost** For Tests: Outside Ancillaries
		Total			

(Total ancillary costs for A days divided by A days equals average research ancillary cost per A day.)

* List all projects (presented and unpresented), including those for which no ancillary support is requested.

** Charges adjusted to cost by category per Patient Care Rate Agreement.

Schedule 2 Category B Inpatient Projects*

Investigator Name	SPID Number	Project Title	Number of Days Per Year	Annual Cost** For Tests: Hospital Ancillaries	Annual Cost** For Tests: Outside Ancillaries
		Total			

(Total ancillary costs for B days divided by B days equals average research ancillary cost per B day.)

* List all projects (presented and unpresented), including those for which no ancillary support is requested.

** Charges adjusted to cost by category per Patient Care Rate Agreement.

Schedule 3 Category A Inpatient Scatter-bed Projects*

Investigator Name	SPID Number	Project Title	Number of Days Per Year	Annual Cost** For Tests: Hospital Ancillaries	Annual Cost** For Tests: Outside Ancillaries	Annual*** Scatter-bed Research Nurse Hours
		Total				

(Total ancillary costs for A scatter-bed days divided by A scatter-bed days equals average research ancillary cost per A scatter-bed day.)

* List all projects (presented and unpresented), including those for which no ancillary support is requested.

** Charges adjusted to cost by category per Patient Care Rate Agreement.

*** Only include hours of nurses paid directly by the GCRC grant, not nurses included in a per diem charge.

Schedule 4 Category B Inpatient Scatter-bed Projects*

Investigator Name	SPID Number	Project Title	Number of Days Per Year	Annual Cost** For Tests: Hospital Ancillaries	Annual Cost** For Tests: Outside Ancillaries	Annual*** Scatter-bed Research Nurse Hours
		Total				

(Total ancillary costs for B scatter-bed days divided by B scatter-bed days equals average research ancillary cost per B scatter-bed day.)

* Include in this Schedule all projects (both presented and unpresented). Include both those projects that involve scatter-bed B days (with entries to be made in all columns)and those scatter-bed B projects for which there are no ancillary costs charged to the GCRC grant (with no entries to be made for days and ancillaries, but entries to be made for the other columns).

** Charges adjusted to cost by category per Patient Care Rate Agreement.

*** Only count hours of those nurses paid directly by the GCRC grant.

Schedule 5 — Category A Outpatient Projects*

Investigator Name	SPID Number	Project Title	Average Duration of Visit	Number of Visits Per Year	Annual Cost For Tests**: Hospital Ancillaries	Annual Cost For Tests**: Outside Ancillaries
			Total			

(Total ancillary costs for A visits divided by A visits equals average research ancillary cost per A visit.)

* List all projects (presented and unpresented), including those for which no ancillary support is requested. Also include off-site research visits in this table.

** Charges adjusted to cost by category per Patient Care Rate Agreement.

Schedule 6 — Category B Outpatient Projects*

Investigator Name	SPID Number	Project Title	Average Duration of Visit	Number of Visits Per Year	Annual Cost For Tests** Hospital Ancillaries	Annual Cost For Tests** Outside Ancillaries
				Total		

(Total ancillary costs for B visits divided by B visits equals average research ancillary cost per B visit.)

* List all projects (presented and unpresented), including those for which no ancillary support is requested.

** Charges adjusted to cost by category per Patient Care Rate Agreement.

Schedule 7 Category D Inpatient Projects

Investigator Name	SPID Number	Project Title	Number of Days Per Year	Industrial Sponsor

Total

Schedule 8 — Category D Outpatient Projects

Investigator Name	SPID Number	Project Title	Average Duration Of Visit	Number of Visits Per Year	Industrial Sponsor	Dollars Projected To Be Credited To The Grant
					Total	

[Note that in the Schedules on the preceding pages, numbers of days and visits projected annually for each project are to be entered. Make sure that the numbers are consistent between these Schedules and other places in the application where such data for these protocols are given again.]

B. Budget for Entire Proposed Period of Support: Provide a justification for any changes, as explained in Form PHS 398.

Additional Pages
(Form PHS 398)

PART II. BIOGRAPHICAL SKETCHES

Arrange the biographical sketches in alphabetical order. Provide biographic sketches in the format of the PHS 398 for the PI, the PD, Associate and Assistant PD, all professionals for whom salary support is requested, and the PI and co-investigators of those projects in the application to be presented at the site visit. For each project in the application not to be presented at the site visit, only the biographical sketch of the PI is required; inclusion of a biographical sketch for any co-investigator is optional.

PART IIA. AMENDED APPLICATION INTRODUCTION

If this is an amended (revised) application, see page 16 of the PHS 398 instructions (Rev. 09/2004).

PART III. RESOURCES AND ENVIRONMENT

A. Background and Introductory Statement

This section describes the institutional environment for research, both current and historical. Relevant information may include the following:

1. Brief description of the origin of the institution and its past contributions to research, especially clinical research (limited to one page);

2. Description of the interaction between basic science and clinical departments;

3. Components or affiliates of the institution relevant to the proposed clinical research effort: graduate schools, medical and dental schools, schools of allied health science, hospitals, research laboratories, and government institutions;

4. Current assets for research: number of full-time faculty members involved with research, current annual grant and contract support, major endowment funds, funded Centers, etc;

5. Patient resources available for research: population and catchment area and number of admissions, inpatient days, and outpatient visits provided by the hospital or medical center;

6. Institutional assets for research training: number of medical and dental students, allied health science students, house officers, and postdoctoral fellows; nature of institutional funds for training; and

7. In competing renewal applications, provide a description of changes in the GCRC since the previous renewal, including responses to weaknesses cited in the previous summary statement.

B. Organizational Framework

The organizational structure of the institution should be defined as it relates to the GCRC, including the chain of professional and administrative responsibility. If these relationships involve another corporate entity (hospital, medical school, research institute, local government, etc.), describe the lines of authority and submit a letter of agreement signed by the responsible officer of each organization that supports the grant stating that the research area will be available on a continuing basis.

C. Administration

Describe the administrative structure under which the GCRC will operate, including the responsibilities of the PD(s), the GAC and its Subcommittees, and any other Committees with advisory roles on specific aspects of the GCRC's clinical research projects, such as the IRB. Provide a membership list, with academic titles, for each committee. Describe the administrative relationship between the PI, PD, and GAC.

Indicate the procedures for coordination among PI, PD, GAC, and individual investigators regarding patient care responsibilities and review and approval of submitted research projects. Describe the process for peer review or audit of the classification of research patients as Category A, B, and/or D. Describe the process by which the GAC reviews and designates industry-related research patients as Category A, B, and/or D. Describe the role of the GAC in overseeing the GCRC budget.

D. Patient Care

Delineate responsibilities for medical care delivery by investigators, and the role of the PD and RSA in the oversight of medical care and research projects. Describe existing mechanisms to assure compliance with IRB-approved projects and witnessing of informed consent. Describe role of interns, residents, and fellows in patient care and emergency coverage.

E. Training and Career Development

Describe the role of the GCRC as an institutional resource in the clinical research training and career development of physicians, dentists, nurses, biostatisticians, and others. In competing renewal applications, summarize work by previous and current CAPs, Minority Clinical Associate Physicians (MCAPs), K12 and K23 awardees, and others that used the GCRC (whether funded by NCRR or another NIH Institute), as well as their publications that cited the GCRC, current academic positions, research support, and percent of effort devoted to basic and clinical research, teaching, patient care, and administration. If funds are requested for a "Mentored Medical Student Clinical Research Program" (whereby a medical or dental student could take time off from medical school to engage in a mentored program of up to one year, including supervised participation in clinical research, didactic coursework related to patient-oriented research, and/or acquisition of laboratory skills that can be applied to patient-oriented clinical research efforts), the following information should be provided: selection method (by the GAC or another committee constituted for this purpose); selection guidelines including eligibility of students and mentors, and the student's plan for research, didactic coursework, and/or acquisition of laboratory skills; evaluation plan; results over the past five years including number of students funded each of these years, name of student and mentor, what was accomplished, and their current activities. If the institution has received a K30 or K12 award, describe how the GCRC is involved. Information in this section of the application may cross-reference Table B below.

F. Core and Other Specialized Laboratories

The primary functions of a Core Laboratory are to provide sophisticated support to ongoing GCRC protocols and to develop or validate new methods for this purpose. In addition, the laboratories may provide clinical research training for investigators, fellows, students, and technicians. Core Laboratory requirements vary widely. Some GCRCs may not need a full Core Laboratory; rather, only a small sample-processing area may be required.

In general, routine tests, such as blood chemistries, hematologic determinations, and urinalyses that are available in the hospital's clinical chemistry laboratories or in another Medicare-approved clinical chemistry laboratory, are not performed in the GCRC Core Laboratory; rather, they are supported through ancillary funds. However, such tests may be performed in the GCRC Core Laboratory when this is critical for timeliness, when an extreme degree of accuracy is needed, or if patient safety is at stake. Cost sharing of Core Laboratory functions should be sought from the funded investigators.

The GAC is responsible for reviewing the Core Laboratory to ensure that its activities are serving the research needs of a wide array of investigators, that tests performed are not routine, and that priorities are set for the use of the Laboratory when concurrent demands exceed the Laboratory's capacity. In all cases, NIH-supported investigations are to be given the highest priority.

The application should justify the requested Core Laboratory resources in terms of the resource needs of the investigators. Examples of requested Core Laboratories include those used for mass spectrometry determinations, magnetic resonance imaging, body composition determinations, and others. To allow an adequate evaluation of the Core Laboratory request, the following information must be provided, both for the most recent, complete 12-month period for which data are available in a competing renewal application, and as projected in a new or competing renewal application:

1. The types of Core Laboratories and their space and location;

2. Type and number of laboratory analyses performed and proposed for the Core Laboratory and an analysis for each test according to the percentages that have been and are proposed to be performed for each investigator or investigator group. In existing units, laboratory log books may be examined at the site visit;

3. Description of the criteria the GAC will apply for deciding the types of analysis to be performed in the Core Laboratory. The number of investigative groups for whom specialized studies will be run;

4. Relationship to the laboratories of the PD and the Associate/Assistant PDs;

5. Future changes in research direction or expected GCRC activity that may alter Core Laboratory requirements;

6. Role and qualifications of Core Laboratory Director and staff with justification for level of support requested;

7. Training that will be available;

8. A summary of quality control procedures and participation in external testing protocols. If the Core has undergone a certifying review, the dates and results of that review should be described;

9. Means employed to protect patient privacy and confidentiality. Integration with bioinformatics resources; and

10. Support provided by the institution and other grants, and process for determining "cost-sharing."

G. Biostatistical Support

Describe the biostatistical support available to GCRC users. Provide qualifications of the biostatistician, the mechanisms by which the biostatistician will interact with investigators and

other GCRC components, and the role to be assumed in research project design and analysis.

H. Informatics Core

The application should justify the requested Informatics Core resources in terms of the resource needs of the investigators. The Informatics Core is to meet the database needs of GCRC-based investigators, enabling adequate and appropriate systems for data acquisition and distribution. Careful consideration should be given to the system configuration to facilitate investigator access to the software systems. To allow an adequate evaluation of the Informatics Core request, the following information must be provided, either for the most recent, complete 12-month period in a competing renewal application, or as projected in a new application:

1. Provide a narrative justification for the space required to accommodate all functions of the Informatics Core;

2. Provide a narrative justification for the equipment selected and upgrades that are needed. The narrative justification for the system should reflect both the resource need and scientific merit of the GCRC-based research projects conducted by investigators who receive primary research funding from NIH and other peer-reviewed awards. The multi-user resource must reflect multidisciplinary and multicategorical clinical research;

3. Summarize the contributions the Informatics Core will make to the progress of the research projects. All studies utilizing Informatics Core resources must have GAC approval;

4. Describe the future changes in research direction or expected GCRC activity that will impact Informatics Core resource requirements;

5. Describe the selection process and qualifications of the Informatics Core Manager, and justify the level of support that is requested for the position;

6. Provide a description of methods employed to protect the confidentiality, security, integrity and privacy of patients' data. [Note that a discussion of compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule is not required in any NIH grant application. See NOT-OD-03-025.]; and

7. Describe the duties of the Informatics Core Manager, which should include:

   a.) maintaining close interface with the GCRC-supported Biostatistician to facilitate adequate data management and analysis support to GCRC-based investigators;

   b.) maintaining close interaction with Administrative Manager to prepare the administrative components of reports required by NCRR and NIH;

c.) ensuring adequate hardware and software maintenance and upgrades through interactions with informatics specialists and vendors, including negotiation and maintenance of hardware and software contracts;

d.) maintaining security of the physical facility, equipment, data files, and file backups and storage;

e.) instructing and assisting clinical investigators in the use of Informatics Core resources. However, the Informatics Core Manager is not required to carry out routine data entry or analyses for investigators or the GCRC Biostatistician; and

f.) administering the resources for the Informatics Core, including ordering of supplies and upgraded equipment. Charges to Informatics Core users are not allowable for Category A and B research. Prorated fees for Category D research and off-center clinical research are to be collected and credited to the patient care category of the GCRC grant.

I. Physical Resources and Utilization

Describe the GCRC facility in sufficient detail to identify each physical component. Include schematic line drawings, reduced to the size of the continuation pages, and identify the size and use of each room. Indicate the proposed room arrangement and use if renovation is proposed.

If space charges are proposed as a separate cost or as part of the routine cost, include a list detailing use and square footage of each room/area to be on the GCRC. If there are GCRC areas that will not be charged to the grant, indicate which areas. In addition, provide a tabular list of rooms to be used for inpatient and outpatient studies. Whether the outpatient area is separate from inpatient area or if inpatient rooms are also used for outpatient visits, indicate which rooms, projected number of visits, length of visits, and average number of hours per day and days per week.

J. Other Existing or Planned Resources for Clinical Research

Attach a brief description of all available or projected facilities for clinical research at the institution and affiliated institutions; for example, GCRCs, categorical Clinical Research Centers, privately funded research wards, etc. Describe the location and number of beds in these facilities, and explain their projected relationship to the GCRC.

K. Data and Safety Monitoring Plan

Provide a description of the GCRC's overall DSM Plan, including any GCRC-wide policies and procedures for establishing, monitoring, and evaluating protocol DSM plans. The overall GCRC DSM Plan must state that each GCRC protocol will have an individual GAC-approved

DSM plan. The overall DSM Plan must state that for all protocols that place participants at significant risk, a DSMB will be included in the protocol DSM plan. The charter (or list of the responsibilities, meeting frequency, etc.) and membership of any DSMB, as detailed in the NIH Guidances on Data and Safety Monitoring, must be included in the DSM plan of any protocol that utilizes a DSMB. Describe in this section of the application the process for initial review, implementation, oversight, and continuing review of protocol DSM plans. Provide details concerning the GCRC's policies and procedures for monitoring and handling of adverse events and serious adverse events that occur on GCRC protocols.

Each protocol DSM plan must be part of the investigator application and be reviewed and approved by the GAC. It is only required that a copy of the protocol DSM plan be included in the new or renewal GCRC application for the seven protocols to be presented at the site visit. DSM plans may also be included in the GCRC application for the unpresented protocols. When included in the GCRC application, the DSM plan should be placed at the end of the protocol. If a DSM plan is not included in the application, it must be available at the site visit for examination by the site visitors.

L. Clinical Research Feasibility Funds (CReFF)

If funds are requested for a CReFF program, provide information on guidelines for eligibility, selection criteria, and an evaluation plan. Also provide for each recipient of CReFF funds over the past five years: name and faculty rank; title of project; dates of funding; funds received; accomplishments and publications.

M. Data Sharing Plan

The Final NIH Statement on Sharing Research Data (NOT-OD-03-032, February 26, 2003) states that "Starting with the October 1, 2003 receipt date, investigators submitting an NIH application seeking $500,000 or more direct costs in any single year are expected to include a plan for data sharing or state why data sharing is not possible." All new and competitive renewal GCRC applications are, therefore, required to include a section in the application to be entitled, "Data Sharing Plan." Please see the NIH Data Sharing Policy. (The Data Sharing Plan will not be evaluated in the scientific merit review of the application.)

N. Research Subject Advocate (RSA)

Provide details of the activities and responsibilities of the RSA(s) at your GCRC. In particular, describe activities/responsibilities related to: consultation with and education of the GAC, PD, investigators, nurses, laboratory and other core personnel related to human subjects protection issues on the GCRC; counseling research participants; DSM plans; safety monitoring, including adverse events/serious adverse events; policies and procedures to enhance protection of human subjects on the GCRC; and liaison with institution human subjects protection offices, including IRBs. Responsibility assigned to the RSA may be divided among two or more qualified

individuals. Provide the name, degree (e.g., M.D., R.N., Ph.D.), and effort funded by the GCRC grant (e.g., 0.5 FTE) for these individuals. Describe the training and experience of each which qualify him/her for this role. If more than one individual is fulfilling the RSA role, discuss the division of responsibilities among them. Discuss the reporting arrangements and experience to date, regarding the reporting of the RSA to the PI of the GCRC grant (or to the PI's designee).

Section 2
(Form PHS 398)

PART IV. RESEARCH PLAN

A. Accomplishments

In competing continuation applications, or in applications for support of a GCRC that has been funded previously from other sources, summarize scientific accomplishments from use of the GCRC since the last review. This will be a factor in the evaluation of the GCRC. Accomplishments selected should represent advances or achievements that led to the prevention of disease, provided a better understanding of a disease process or of a physiologic mechanism, provided a new or better therapeutic approach, or resulted in a new methodology either for the early detection or diagnosis of disease. Describe outcomes of clinical trials. Describe contributions to multicenter trials. The narrative should describe clearly each accomplishment, its originality, and its significance in terms of the above categories. For each accomplishment, provide the relevant publication reference(s). State if the accomplishment has found application in the health care system. Describe any findings that result in more cost-effective approaches to diagnosis or therapy. Describe not only the scientific accomplishments but also the GCRC support that was provided for these studies (days, visits, core laboratory, etc.). Include information for all years since the last competitive renewal. The Accomplishments section should not exceed five pages.

B. Center Bibliography (Competing Continuation Applications Only)

For Center renewal applications, cite only published papers that used GCRC resources. Include scientific articles that resulted in whole or in part from investigations undertaken with GCRC resources since the last funded application. Omit publications that are in press, papers that have been submitted but not yet accepted, and papers in preparation. Include names of all authors in the same order as they appear in the journals, as well as titles of articles, volume numbers, inclusive pages, and year of publication. Asterisk those papers that cited the GCRC, i.e., either mentioned use of the GCRC in the text, or cited the GCRC (M01) grant number. For each project that is not asterisked, indicate as least one type of GCRC resource that was used for completion of the work included in the paper (e.g., category A inpatient days, category A outpatient visits, core laboratory).

Review articles, books, and abstracts may be cited, but they should be listed separately.

C. Research Projects

Include all research projects proposed for use of the GCRC that are expected to be active in the first year of the grant, if funded, including projects already underway at the time of the application. List them by project PI, in alphabetical order. Exclude projects that will be completed by the start of the new funding period. All projects should be included, even if they are awaiting approval by the GAC or the IRB at the time of submission of the application. Indicate in the page index at the beginning of this section those projects not yet approved at the time the application is submitted.

Presented Protocols

In the application, the length of each of the seven projects selected for presentation at the site visit may not exceed 25 pages. These page limitations are inclusive of Specific Aims, Background and Significance, Progress Report and Preliminary Studies, and Research Design and Methods sections. Each project should include a clearly identifiable hypothesis, brief background information, and an in-depth narrative of the methodology to be employed. Provide details of biostatistical design and analysis for each project.

In addition to the 25-page limit (for the sections on: Specific Aims; Background and Significance; Preliminary Studies/Progress Report; and Research Design and Methods), the following also must be provided with no page limitation: 1.) a current bibliography that supports the hypothesis, background, and methodology, including references to papers and abstracts that have resulted from previous work by the investigator submitting the project and references to the work of others; 2.) a section entitled "Human Subjects Research and Protection from Risk," with subheadings to address the four issues described on page 11 and 12 of part II of the PHS 398 Instructions (revised 09/2004); 3.) a section on Inclusion of Women and Minorities as described on pages 14-18 of part II of the PHS 398 Instructions, including the "Targeted/Planned Enrollment Table" for all protocols and "Inclusion Enrollment Report" for those protocols which have already enrolled any subjects; and 4.) a section on Inclusion of Children as described on pages 19 and 20 of part II of the PHS 398 instructions (revised 09/2004).

In addition, for each project, provide a justification for utilization of GCRC resources, along with an estimate of the number of research patients to be studied and the number of research inpatient days and outpatient visits (categories A, B, and D), and other GCRC resources (e.g., Core Laboratory, Informatics Core , etc.) to be used in the first year of the new project period. Also, provide the same information for actual usage during the last twelve-month period for which data are available. Provide a summary of anticipated ancillary charges for each project. Additionally, provide a summary of other research needs to be provided by the individual investigator's laboratory or outside laboratories. Federal and non-Federal grants, contracts, or

other support held by investigators conducting the proposed study should be identified by project, together with an indication of whether they relate directly to the proposed study. Indicate the grant/contract number, source of support, and inclusive period of support.

In addition, include a copy of the DSM plan.

Each project in the application to be presented at the site visit must be accompanied by a brief (one-half page) abstract or summary of the project. The abstract will serve as the basis for the description of the proposal that will be incorporated into the Site-Visit Report reviewed subsequently by the Clinical Research Review Committee, and the Summary Statement reviewed subsequently by the NARRC.

Unpresented Protocols

While each of the seven protocols to be presented at the site visit may be up to 25 pages in length, the other (unpresented) protocols may be as short as one page. Include the following: title; subproject identification (SPID) number; PI; co-investigators; peer-reviewed funding supporting this protocol; dates of IRB and GAC approval; GCRC utilization (i.e., number of A, B, and D days and visits, core laboratory usage, ancillary costs, etc.) both in the last twelve-month period for which data are available (actual), and the first year of new project period (projected); hypothesis, goals, and methods; progress report; future plans; and publications that have already resulted from this study. Subsequently, the following also must be provided: 1.) a section entitled "Human Subjects Research and Protection from Risk," with subheadings to address the four issues described on pages 11 and 12 of part II of the PHS 398 Instructions (revised 09/2004); 2.) a section on Inclusion of Women and Minorities as described on pages 14-18 of part II of the PHS 398 Instructions, including the "Targeted/Planned Enrollment Table" for all protocols and "Inclusion Enrollment Report" for those protocols that have already enrolled any subjects; and 3.) a section on Inclusion of Children as described on pages 19 and 20 of part II of the PHS 398 instructions (revised 09/2004). Regarding the three items above (Protection of Human Subjects, Inclusion of Women and Minorities, or Inclusion of Children), if such information for this protocol was previously submitted to NIH, either in a grant application that was subsequently funded or in a grant Progress Report, it is sufficient to cite that submission; for example, "For this protocol, information regarding Protection of Human Subjects was provided in the funded grant application 2 R01 HL03099-16;" "For this protocol, information regarding Inclusion of Women and Minorities was provided in the Progress Report for grant 5 U01 AI07782-08;" "For this protocol, information regarding Inclusion of Children was provided in the funded grant application 1 R01 DK20103-01."

PART V. TABLES

TABLE A. Faculty Member Research Participation (Instructors and above). List the number of faculty members in each Department and their percent of effort devoted to research.

Example
TABLE A
Faculty Member Research Participation

Number of Faculty Members			Number of Faculty Members Devoting the Indicated Percent of Effort to Research	
DEPARTMENT	FULL-TIME	*PART-TIME	5 - 50	Above 50
Medicine				
Surgery				
Ob-Gyn				
Pediatrics				
Other Clinical Departments				
Pre-Clinical Departments				
TOTALS				

*Salaried

TABLE B. Training. Complete Table B, below. Do not include house officers (interns and residents).

Example
TABLE B
Fellows in Training

DEPARTMENTS	Number of Post-Doctoral Fellows	
	M.D.	Ph.D. or equivalent
Medicine		
Surgery		
Pediatrics		
Ob-Gyn		
Other Clinical Departments		
Pre-Clinical Departments		

1. Provide a list of all funded institutional training grants by department or division, including grant numbers, PIs, funding sources, and inclusive dates of support.

2. For competing continuation applications, provide the name(s) of all CAPs, MCAPs, and K12 and K23 awardees supported at the GCRC at present and in the past ten years, inclusive dates of support, specialty, and a description of their current professional activities and academic affiliations. If possible, provide information as to whether those individuals are currently funded as PIs or co-investigators of research grants.

3. Provide a description of the opportunities for medical students to work with GCRC-based investigators and their projects. Provide a summary of medical students supported by GCRC-based investigators. Separately, provide a detailed list of medical students (by name and year) supported totally or in part by GCRC resources since the time of previous GCRC review.

TABLE C-1. Utilization of the Center, Last Three Years (for competing continuation applications and applications from Centers previously funded from other sources). Indicate the number of Category A and Category B days on the Center, scatter-bed days off the Center, and outpatient visits for each of the last three years of the grant. Provide the average length of patient stay. Centers with separate adult and pediatric units subsumed under one grant must submit separate tables for each unit.

Example

TABLE C-1

Utilization of the Center, Last Three Years

INPATIENT DAYS

Year	Category A	Category B	Scatter Bed A	Scatter Bed B	Category D	Category C	Average Length of Category A Inpatient Stay
2000-2001							
used:	1,100	1,200	25	300	400	0	4.5 days
awarded:	1,090	1,220	25	100	400	0	
2001-2002							
used:	etc.						
awarded:							
2002-2003							
used:	etc.						
awarded:							

Indicate number of days for all categories.
Category A: Research patients or normal controls.
Category B: Patients receiving established medical care and participating in a research project. All research costs are paid by the GCRC or from the investigator’s research support.
Category D: Industry-initiated research project. All charges paid by industry directly to institution.
Category C: Non-research patients who are boarders on discrete Centers.

Example
TABLE C-2
Utilization of the Center, Last Three Years

OUTPATIENT VISITS

Year		Outpatient Visits A	B	D
2000-2001	< 1 hour	500	500	500
	1 - 3 hours	500	500	500
	3 - 6 hours	75	75	75
	6 -10 hours	75	75	75
	>10 hours	75	75	75
	TOTAL (USED)	1,225	1,225	1,225
	AWARDED	1,000	1,000	1,000
2001-2002	< 1 hour	500	500	500
	1 - 3 hours	500	500	500
	3 - 6 hours	75	75	75
	6 -10 hours	75	75	75
	>10 hours	75	75	75
	TOTAL (USED)	1,225	1,225	1,225
	AWARDED	1,000	1,000	1,000
2002-2003	< 1 hour	500	500	500
	1 - 3 hours	500	500	500
	3 - 6 hours	75	75	75
	6 -10 hours	75	75	75
	>10 hours	75	75	75
	TOTAL (USED)	1,225	1,225	1,225
	AWARDED	1,000	1,000	1,000

TABLE D-1. Principal Users of the Center (for competing continuation applications and for applications from GCRCs previously funded from other sources). List approximately ten investigators who have used the most research inpatient days and outpatient visits by grant year for the last three grant years. Provide Category A, B, and D days and outpatient visits separately. If investigators have left the institution, footnote the year of departure.

Example
TABLE D-1
Principal Users of the Center

INPATIENT DAYS

		2000-2001					2001-2002					2002-2003				
Investigator	Department	Category			Scatter-bed		Category			Scatter-bed		Category			Scatter-bed	
		A	B	D	A	B	A	B	D	A	B	A	B	D	A	B

M01-RR-_____ Principal Investigator/Program Director:_____

Example
TABLE D-2
Principal Users of the Center

OUTPATIENT VISITS

		2000-2001			2001-2002			2002-2003		
Investigator	Department	Category			Category			Category		
		A	B	D	A	B	D	A	B	D

TABLE D-3
Principal Users of Ancillary Costs

TABLE D-3. Principal Users of Ancillary Costs (for competing continuation applications). List, in descending order, the 10 protocols that used the most ancillary costs in the grant year that was reported on in the latest submitted annual report.

SPID	Investigator	Protocol Title	Ancillary Costs Used

TABLE E. Proposed Scientific Agenda for the Site Visit and Abstract Package.

For each of the seven projects to be presented at the site visit, provide the following information:

1. The title of the project and the page number on which it begins in the application;

2. The name, degree (M.D. or Ph.D.), and title of the PI and all co-investigators, and the page numbers on which their biographical sketches begin in the application;

3. All sources of funding for each PI and co-investigator (along with percent effort, grant number, grant title, PI of the grant, inclusive dates, and approximate current annual dollar amount) supporting the work of these investigators, regardless of whether the funding is related to the project to be presented at the site visit. Asterisk those sources of funding that directly support at least some aspects of the research project. Include support from portions of Program Project and Center grants;

4. List the resources from the GCRC (inpatient days and outpatient visits by category, ancillary costs, Informatics Core, RSA, Core Laboratory, biostatistician, and bionutrition research) projected in the first year of the new project period. In competing applications, include the actual resources used in the last twelve-month period for which data are available; and

5. Provide one-half page abstract of the project.

EXAMPLE
Proposed Scientific Agenda for the Project Site Visit

Clinical Studies of the Mechanism of Spherical Missile Transfer (Protocol p. 372)

Joseph B. Tinker, M.D., Professor of Surgery (C.V. p. 119)

John S. Evers, M.D., Ph.D., Associate Professor of Anesthesiology (C.V. p. 44)

Frank L. Chance, M.D., Assistant Professor of Medicine (C.V. p. 29)

NCI Program Project P01 CA67182; Dr. Chance 15% effort

A Study of Molecule X in Disease Y
(PI of Program Project, Harry M. Steinfeldt, M.D.)
(Jan. 1, 2000 to Dec. 31, 2004; annual budget $250,000)

Resources required: (annually)	130 Category A inpatient days 75 Category B inpatient days 10 Category A scatter-bed days 50 Category A outpatient visits (1-2 hours) 10 Category A outpatient visits (10-12 hours) 50 Category B outpatient visits Informatics Core Core Laboratory (200 insulin determinations) Biostatistician Bionutrition Research Ancillary Costs ($2,500)

Abstract of project.

Section 3
(Form PHS 398)
Appendix

Do not include substantive materials in appendices.

SITE-VISIT INFORMATION

I. SITE-VISIT DATE

The SRA of the Clinical Research Review Committee is responsible for determining the need for a site visit. He/she, or another SRA in NCRR's OR, will be assigned to organize the site visit. In general, new and renewal GCRC applicant institutions will be site-visited. Occasionally, if needed, institutions submitting a complex supplementary application may be site-visited. In some cases, an "applicant interview" (reverse site visit) may be held. Site-visit dates are scheduled by the OR, usually months prior to submission date of the grant application. Site visits usually take place between 30 and 80 days after the receipt date of the application; PDs should alert investigators who will be presenting at the site visit of this time frame. Once the site-visit date has been established, the site-visit SRA will be in contact with the GCRC Administrative Manager regarding possible hotels for the site visitors. The actual booking of the hotel will be done by the site-visit SRA and should not be done by the GCRC Administrative Manager. Once the hotel has been booked by NCRR, the site visit cannot be rescheduled.

II. ADVANCE MATERIAL

Material to be Submitted Prior to Submission of the Application (Due Date Set by the Site-Visit SRA)

Additional information is required to supplement the application and to allow for the preparation of the site visit. The following information should be sent directly to the site-visit SRA: 1.) a copy of the proposed site-visit agenda and abstract package, containing the project information from Table E of the application and arranged according to the schedule described below; and 2.) a diskette containing the abstracts of the protocols to be presented at the site visit. Alternatively, this information may be submitted electronically. Indicate building, room number, and address where the site visit will be held. Applicants are encouraged to examine Supplement III to the GCRC Guidelines, "Information and Instructions for Site Visitors on a GCRC Site Visit," so that they will be aware of the kind of information reviewers will be seeking.

Material to be Submitted After Submission of the Application But Prior to the Site Visit (Due Date Set by the Site-Visit SRA)

Two copies of the consent forms for all of the IRB-approved protocols in the application must be sent to NCRR's OR. These consent forms will then be sent out to the site visitors for their review prior to the site visit. If the title of a consent form is not identical to the title of the corresponding protocol, or if there is more than one consent form for a given protocol, or more than one protocol for a given consent form, this must be clearly indicated when the consent forms are submitted to the OR. In addition, if there is a recently proposed addition to a protocol and the revised consent form incorporating that addition has not yet been IRB approved, this must be indicated clearly when the consent forms are submitted to the OR. Indicate the IRB number and protocol number on the consent form. Provide a master list index of all consent forms indicating the date of initial IRB approval and the date of the most recent annual IRB re-approval of the protocol. If a protocol does not yet have IRB approval and therefore does not yet have an IRB-approved consent form, include a page stating that, in lieu of providing the consent form for that protocol.

III. SITE-VISIT AGENDA for most GCRCs

The following is a suggested site-visit schedule.

DAY 1 (on site):

7:45 a.m.	Preliminary executive session of site visitors.
8:15 - 10:45 a.m.	Presentation by Program Director and others (see below)
10:45 - 11:00 a.m.	Break
11:00 a.m.	Administrative meeting of administrative reviewer with institutional officials (concurrent with scientific presentations)
11:00 - 11:30 a.m.	Scientific Presentation #1

11:30 - 12:00 noon	Scientific Presentation #2
12:00 - 12:30 p.m.	Scientific Presentation #3
12:30 - 1:15 p.m.	Lunch
1:15 - 2:00 p.m.	Tour of Facilities
2:00 - 2:30 p.m.	Scientific Presentation #4
2:30 - 3:00 p.m.	Scientific Presentation #5
3:00 - 3:30 p.m.	Scientific Presentation #6
3:30 - 4:00 p.m.	Scientific Presentation #7
4:00 - 4:15 p.m.	Break
4:15 - 6:30 p.m.	Executive Session

DAY 2 (off site):

7:30 - 11:30 a.m.	Executive Session

The site-visit agenda may be modified to allow time for site visitors to review some unpresented protocols and corresponding consent forms.

Questions arising during the executive session may require a meeting with the PD, who should remain available until the site-visit team leaves the institution.

The two-and-a-half hours (8:15 a.m. - 10:45 a.m.) allowed for presentations by the PD and others is usually begun by a short presentation by the GCRC PI; there may be other introductory speakers (e.g., CEO of the Hospital, Vice-Chancellor of the University, elected officials), but it is suggested that these presentations be limited to a total of 10 minutes. The PD (with assistance from, for example, the Associate PD, RSA, Core Laboratory Director, Informatics Core Manager, and other members of the GCRC staff, as desired) should use the remaining time to cover the following topics: Accomplishments; GCRC resources utilized since the last review; Response to critique in previous summary statement; Innovations since last review; Satellites; Core Laboratories; Biostatistics; Nursing; Patient Care; Bionutrition; Informatics; Training and Career Development; Center Management; RSA; Justification for current request; GAC; IRB; Physical Facility; DSM Plan; and CReFF funds. All the above issues should be addressed; however, the PD may choose to arrange these presentations in a fashion that he/she believes will best highlight this GCRC, including the order, timing, and individual chosen to address a given topic, and with the option to

reserve some of this time for a wrap-up session later in the day. Adequate time should be left for questions from the site visitors.

IV. SCIENTIFIC CONTENT

The seven projects presented should account for a significant fraction of requested inpatient days and outpatient visits and also reflect requests for other resources (Informatics Core, Core Laboratory, Bionutrition, etc.). Industry-initiated projects shall not be presented at the site visit; multicenter trials may be presented only if the investigator at your institution originated the trial or has added unique features to the project, not being conducted at other Centers, and only after discussion with the site-visit SRA.

A. Project presentations are to be hypothesis-oriented investigations requiring a significant number of inpatient days, outpatient visits, or Core resources.

B. Scientific presentations should be limited to 15 minutes, with 15 additional minutes for discussion by the site visitors with the investigators.

C. Presentations may begin with a brief review of previous work (no more than five minutes) but should proceed rapidly to a clear statement of the questions proposed for future investigation. The experimental project should be described in some detail. Each presentation should consist of a description of how the GCRC will be used for the research project and a justification for requested resources (e.g., number of research inpatient days or outpatient visits by category, Informatics Core, etc.), and preliminary data.

V. ADMINISTRATIVE REVIEW

During the site visit, the consulting administrator (sometimes accompanied by an NCRR staff representative) will meet with hospital and university officials to discuss budgetary and management procedures, physical facilities, staffing, personnel functions, and other operations pertinent to the unit; they also will discuss GCRC operations with the Head Nurse, Research Bionutritionist, and Administrative Manager. These discussions will be held separately from, but concurrently with, the scientific presentations. Architects and plant management personnel should be present when changes in the physical facility are requested.

VI. ADDITIONAL SITE-VISIT MATERIAL

To aid reviewers, the following information must be available for examination during the site visit.

A. Consent forms for all projects that were listed in Schedules 1-8 that have IRB approval.

B. For GCRC protocols with industry support, copies of documents that the GAC reviewed when

deciding whether the protocol was category A or category D. Documents are to be available for both investigator-initiated and industry-initiated projects.

C. IRB records, including minutes. Site visitors are representatives of the DHHS and, as such, are authorized to inspect and copy IRB records at reasonable times and in a reasonable manner. It is essential that the representatives be given sufficient access to records to assure themselves that IRB activities are being carried out in accordance with the Federal Regulations for the Protection of Human Subjects, as described in 45 CFR 46.

D. GAC meeting minutes for at least the past three years.

E. A complete copy of each protocol (both "presented" and "unpresented") that was listed in Schedules 1-8, exactly as it was approved by the IRB.

F. Tabular summary of requested annual Categories A, B, and D research inpatient days and Categories A, B, and D outpatient visits by project for those presented at the site visit, as well as a separate table for those projects not presented. Indicate whether the Core Laboratory or Informatics Core resources are requested for each project.

G. Inpatient occupancy and outpatient statistics for the months since Table C was prepared.

H. Biographical sketches of all key personnel affiliated with the GCRC, including new arrivals since the application was submitted. Include PIs and all co-investigators on all (presented and unpresented) protocols that were listed in Schedules 1-8.

I. If the individual DSM plans for each protocol in the application were not included in the application, they must be available for examination during the site visit.

J. Copies of scientific journal publications that credited support by the GCRC grant.

National Center for Research Resources
National Institutes of Health
Department of Health and Human Services

Division for Clinical Research Resources

Guidelines for the General Clinical Research Centers Program (M01)

Supplement IA: Instructions for Preparing a GCRC Supplemental Application

April 2005

An Administrative Document Issued by the
National Center for Research Resources (NCRR)

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Division for Clinical Research Resources

INSTRUCTIONS FOR PREPARING A GCRC SUPPLEMENTAL APPLICATION

I. TYPES OF SUPPLEMENTS

Funded GCRCs may request supplemental funds. In general, requests for small increases in the budget may be handled administratively without peer review (an administrative supplement). Larger requests–including requests for new satellites, resources, or cores (e.g., informatics or imaging cores)–will be peer-reviewed as competing supplements. In all cases, applicants must consult with staff in NCRR's DCRR before submitting the supplemental request.

II. COMPETING SUPPLEMENTS

Occasionally, GCRC supplements are solicited by NCRR, and the guidelines for those will be described in a Request for Applications or Program Announcement. All text below refers to unsolicited competing supplements.

A. Competing supplemental requests will not be accepted without approval, given at least six weeks prior to the anticipated submission, by the DCRR. The format and review of supplemental grant applications are similar to those of new and renewal GCRC grant applications, except that the information to be included (projects, biographical sketches, tables, etc.) may be limited to that required to justify the items requested in the supplemental application. The deadline receipt dates for supplemental applications are the same as those for new and renewal GCRC applications. Site visits are not usually required for supplemental applications, unless the applications are complex or require additional assessment of GCRC resources.

B. When preparing a competing supplemental application, follow the format as prescribed for Parts I - IV on page I-6 of these DCRR Guidelines. Include all specified "Resources and Environment" sections (e.g., Patient Care, Physical Resources and Utilization, DSM Plan), even if the text in some of these sections is extremely brief. As specified in the PHS 398 instructions, the supplemental application must be complete so that it can be evaluated by a peer-review committee, without the need to refer to the "parent" GCRC grant application.

C. Clearly justify the need for the requested new core or resource. For example, describe the accomplishments of the "parent" GCRC without the core; then, describe the projected impact of the new core. Identify the investigators who will use the new core, and indicate the amounts and sources of their peer-reviewed support. The investigators should span diverse disciplines and have independent peer-reviewed support. Provide information about the protocols and/or investigators that will utilize the new core either in the application or in an appendix to the application. (See Section I below.) A core might serve, for example, clinical and/or biostatistical and/or laboratory-only protocols. A core that only supports a few investigators requires special justification. Describe any

contraction of effort or de-emphasis of existing programs within the GCRC that may or will occur as a result of this supplement.

D. If similar resources already exist at the institution, explain how the proposed GCRC facility will enhance or complement them. Explain how the proposed core will bring "added value" to the entire GCRC, rather than benefiting only a few investigators. Describe or estimate any cost savings the core might achieve over individual investigator-funded operations. Indicate the amount of institutional support that will be provided for this core. If none, this should be clearly stated.

E. Clearly link major resource requests directly to protocols. This includes personnel, space, equipment, software, etc. This could be accomplished using tables, and it is critical for assessing budget requests. Justify budget requests with realistic workload assumptions in support of specific protocols. If anticipated use of resources by investigators at other institutions is cited as a justification for the need for resources, letters documenting the proposed use by, and any financial arrangements with, these parties should be included in the application. Discuss any anticipated generation of program income.

F. Clearly describe how and by whom resources will be allocated and prioritized. Include provisions for supporting junior investigators and pilot projects, as well as established, funded investigators. These provisions may include CReFF funds and other mechanisms for ensuring that junior investigators have adequate access to the proposed core facility or other requested resources.

G. Describe how the resource will be supported. If appropriate, include a plan for cost sharing with, or charge-back of core resources to, investigators. Define rules for providing core resources that are already funded through an investigator's individual grant. In most cases, support for primary outcome measures and data collection and analysis should come from investigators' individual grants. If the proposed core will save costs or provide a better service or other added value, funded investigators should generally provide funds via charge-backs for part or all of the costs of the service. The plan should provide standardized rules that are fair to all investigators, while encouraging new investigators and pilot projects.

H. Describe an administration for the core that is responsible to the GAC and PD. If the core contains facilities or personnel that are shared with non-GCRC investigators, clearly describe how these resources will be administered, while safeguarding against use of GCRC funds for non-GCRC activities.

I. Research projects that have already received GAC review and approval should make up the bulk of the proposed scientific activity for the new core. Pending protocols, or investigative groups who have expressed interest in using the new core but without

GAC-approved protocols, may be described in the application, but they will not be given major weight in the review process. Pilot projects, designed to generate data for peer-reviewed grant applications, are encouraged, and the means of prioritizing them should be clearly presented. Research protocols included in the application should follow the instructions and include all information requested on page I-28 of these DCRR Guidelines under "Unpresented Protocols."

J. For molecular biology/genomics cores, describe the informatics and biostatistical support that will be required. For example, a genotyping or gene expression core is likely to require sophisticated data management and analysis. The availability and suitability of informatics and biostatistical resources should be described, and letters of collaboration from informatics staff should be included in the application. If these resources are not already available, they should be requested and justified in the application.

K. For informatics cores, describe, or include plans to develop, a manual of operations. The existing or proposed manual should include standard operating procedures for establishing and maintaining access/security; system administration; and data backup, disaster recovery, and archiving. There should be institutional support of GCRC staff desktop computers, so that the core spends most of its resources supporting and training investigators. If this institutional support is not available, this should be clearly discussed.

L. For bioinformatics cores, describe the relationship between the proposed bioinformatics core and the existing informatics core. Explain how they will interact in terms of overall data management for protocols. If resources are requested that will provide services/training for other GCRCs, provide data on which centers will use the resource and the projected utilization. If resources are requested to support protocols from other GCRCs, provide specific information about these protocols.

M. Dental satellites may be configured with outpatient visits to be conducted in dental chairs. Requests may be made for a part-time Dental Clinic Manager and Research Dental Hygienist, for Dental Consumable Supplies, and for Space Charge. Informatics Core and other infrastructure elements should be integrated with the main GCRC.

N. Describe the effect that this supplement will have on training efforts.

There is no longer a Supplement II to these Guidelines for the GCRC program. Supplement II previously dealt with the Clinical Associate Physician (CAP) Program, which has terminated, and the Mentored Patient-Oriented Research Career Development Awards.

Information regard the Mentored Patient-Oriented Research Career Development Awards (K23) will soon be available in the "Guidelines for Other DCRR Programs."

National Center for Research Resources
National Institutes of Health
Department of Health and Human Services

Division for Clinical Research Resources

Guidelines for the General Clinical Research Centers Program (M01)

Supplement III: Information and Instructions for GCRC Site Visitors

April 2005

An Administrative Document Issued by the
National Center for Research Resources (NCRR)

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Division for Clinical Research Resources

INFORMATION AND INSTRUCTIONS FOR GCRC SITE VISITORS

I. INTRODUCTION

A project site visit to the applicant institution is part of the evaluation of an application for a GCRC grant. Written critiques from site-visit teams and their recommendations are incorporated into a report that is presented at the next meeting of the Clinical Research Review Committee. This site-visit report is essential to the Committee's evaluation of the application and serves as the basis for its recommendation (Summary Statement) to the NARRC. Following Clinical Research Review Committee action, the Summary Statement, with its priority score, is sent to the PI identified on the application.

II. FACTORS IN THE EVALUATION

Factors considered by project site visitors include: l.) scientific merit, the biostatistical design of the clinical research proposals, and their need for the GCRC; 2.) peer-reviewed funding held by participating investigators; 3.) diversity of scientific areas and interaction between basic and clinical departments; 4.) opportunities for junior investigators to gain expertise, enabling them to become independent investigators; 5.) the collective impact of the individual proposals on clinical research at the institution; 6.) the administration of the GCRC; 7.) the physical facilities of the GCRC; and 8.) the opportunities for medical students, house staff, and fellows for research exposure on the GCRC and participation in research projects. Specific areas should be considered in evaluating these elements. The budget is considered after these evaluations are concluded.

A. Specific Research-Related Factors:

1. **Quality:** whether the research projects are hypothesis-oriented, incorporate adequate biostatistical design, and are likely to provide new scientific information.

2. **Peer-reviewed funding of investigators:** whether a significant number of investigators have independent grant support, especially from NIH or other peer-reviewed funding sources.

3. **Breadth:** the extent to which utilization of the GCRC will be multidepartmental and multicategorical, and whether there is interaction among investigators from multiple disciplines, including basic and clinical departments.

4. **Impact of the Award:**

    a. **Need -** whether the GCRC is necessary for the proposed studies, or whether they could be done as well elsewhere in the institution.

b. Importance - significant new research contributions by GCRC-based investigators and evidence of bidirectional translation of basic and clinical research activities.

c. Resources - the number of research inpatient days and outpatient visits to be provided for scientifically meritorious projects. Assessment of GCRC resources requested for support, and the number, breadth, and quality of projects utilizing the Core Laboratory, Informatics Core, biostatisticians, and research bionutrition resources.

d. Productivity and Accomplishments - the number and quality of scientific articles published by GCRC investigators over the previous five years.

e. Junior Investigators - opportunity for junior physician-investigators to gain the expertise to develop into independent investigators capable of successfully competing for independent research funding. Quality of research proposals submitted by K23 applicants, and the current research activities and research support of previous CAP, MCAP, and K23 awardees.

f. Training and Career Development - the extent to which the GCRC is or will be utilized as a research training environment for medical students, physicians, dentists, technicians, nurses, social workers, bionutritionists, and others, and the quality of the mentorship that will be provided.

g. Industry - relative balance between investigator-initiated and industry-initiated research projects utilizing the GCRC and appropriate categorization of research projects by the local GAC.

B. Physical Facility:

Reviewers will evaluate whether the inpatient and outpatient research areas are suitable for the nature of patient research in the age groups (e.g., infants, adolescents, the aged) and research complexity required for the proposals. In some cases, specialized facilities within the GCRC may be required for patient safety or for specialized studies. Unless otherwise justified, a unit funded under the discrete funding mechanism should be within the main patient-care area of the hospital, close to the administrative offices of the PD and Administrative Manager. The RSA office should be close to the patient-research area to facilitate access to the unit and to facilitate interaction with GCRC staff and research participants. The Informatics Core area should be convenient and efficient, with terminals readily accessible to investigators. The Core Laboratory should be an appropriate size for its function.

C. Administration:

l. **Principal Investigator:** An individual whose authority transcends departmental boundaries, usually the Dean of the medical school to which the GCRC is awarded. The PI appoints the PD and members of the GAC, including its chairperson. The PI derives no salary support from the GCRC award.

2. **Financial Management:** Includes a review of the classification by the GAC of resource utilization into Categories A, B, C, or D, and research subjects as inpatients or outpatients. These classifications are important, because an appropriate use of Categories B, C, and D patients conserves program funds and makes the GCRC operation more cost-effective. Other factors to be considered, primarily by the administrative reviewer, include the quality of the operational relationships between GCRC and institutional staff, the qualifications of the Administrative Manager, and the capacity of the institution to provide adequate cost-accounting data.

3. **Program Directorship:** The PD should be an individual with relevant knowledge, scientific expertise, and evidence of administrative skills. In addition, the PD should be involved in the conduct of GCRC-based research, and be a recipient of independent peer-reviewed research funding. If there are Associate or Assistant PDs, their qualifications, research activities on the GCRC, sources of research support, and their administrative functions are also reviewed. Associate and Assistant PDs are active investigators at the GCRC and recipients of peer-reviewed funding as PIs or co-investigators. PDs and Associate PDs must be licensed physicians. The PD ultimately is responsible for the day-to-day oversight of GCRC activities.

4. **GCRC Advisory Committee:** The composition and functions of the GAC and the content of its minutes (including attendance records) are reviewed. The GAC is directly responsible to the PI and works closely with the PD. The GAC assesses the utilization of GCRC resources–such as inpatient days, outpatient visits, Core Laboratory, Informatics Core, bionutrition research–by investigators and reviews financial management. In addition, the GAC should make a genuine effort to improve the scientific merit of the projects, review biostatistical design, address risk-benefit, safety and ethical concerns, work with the RSA to optimize DSM plans, evaluate projects for proper gender, minority, and children inclusion, and classify all studies as appropriate for Categories A, B, C, or D.

5. **Institutional Review Board:** Membership, attendance records, and minutes of IRB meetings are also examined by reviewers. The minutes should document significant issues discussed and not simply state “approved,” “deferred,” or “rejected.”

6. **Patient Care:** Describes the quality of professional medical and nursing coverage of patients hospitalized on the GCRC or participating in outpatient research. Patient charts should have adequately detailed histories and physical examinations along with progress notes. The project PI or his/her designee should have appropriate notes on the patient

chart in addition to house staff and fellows' notes. A signed informed consent document or a copy should be maintained in the GCRC research or administrative files. All projects being conducted on the GCRC must have received full approval from the IRB and GAC. Reviewers should examine informed consent documents and at least one reviewer will conduct some chart reviews.

7. **Animal Care:** If GCRC funds support animal-related research activities, reviewers should determine whether the proposed use of the animals is justified. If GCRC funds support vertebrate animal research activities, reviewers should assess the adequacy of the response to the five points described in the PHS 398 Instructions.

D. Budget:

The requested budget is organized into the following categories: Personnel, Consultant Costs, Equipment, Supplies, Travel, Patient Care Costs, Alterations and Renovations, and Other Expenses. In general, it is the responsibility of the site visitors to determine whether budgetary items are justified by meritorious scientific projects in the application, not simply whether the costs are properly estimated. For example, the review process should determine how much support for program directorship is justified and how many nurses are required based on the projects approved. Reviewers also should determine whether equipment requests are justified, not simply the equipment costs, and how many inpatient days and outpatient visits are necessary. Ordinarily, no more than 50 percent of the PD's time is supported for the administrative oversight of the GCRC; exceptions are considered on a case-by-case basis. Associate and Assistant PDs also may be supported for administrative oversight, not usually in excess of 25 percent of time for each individual unless unique GCRC needs require support up to 50 percent of time of an established, funded investigator as an Associate Director. In general, support for total program directorship of a GCRC does not exceed l.0 FTE, although this may be exceeded for very large or complex GCRCs. The level of support for laboratory supplies depends on the nature of the technology in the Core Laboratory. Routine chemistries (such as CBC, urinalyses, SMA 24) are not to be supported in the Core Laboratory; rather, they are paid as patient research ancillaries or by third parties if the patient category is B, C, or D. Alterations and renovations may be the subject of cost recommendations by site visitors. Using advice from expert consultants, as needed, these recommendations are based on scientific merit of GCRC-based research, need for the alterations, and cost-effectiveness.

Site visitors are asked to make a recommendation on each request in the application. Decisions should be deferred only if key information that is needed by reviewers is not available but can be provided by the applicant in a reasonable period. A failure of the applicant to provide adequate justification for budget items may result in a recommendation of disapproval, not deferral.

III. SITE-VISIT CONDUCT

A. Nature and Purpose:

The site visitors function as a fact-finding team and group of expert consultants for the Initial Review Group (i.e., the Clinical Research Review Committee.) Usually, two or more members of the Clinical Research Review Committee are among the site visitors, and one of them serves as Chairperson–unless the site visit is a Special Emphasis Panel (SEP). The remainder of the site visitors are scientists with specific expertise for particular areas of research described in the application, and an administrative reviewer. The Chairperson serves as moderator, conducts the executive sessions, and assumes primary responsibility for presenting the application and the report of the site-visit team to the next meeting of the Clinical Research Review Committee.

A member of NCRR's OR attends all site visits as an SRA and provides necessary administrative information to the site-visit team, facilitates the communication between GCRC personnel and the site-visit team, instructs the site visitors in their duties, monitors the process and conduct of the review, disseminates and interprets review policy, collects review materials generated by members of the site-visit team, and formulates the site-visit report for the Clinical Research Review Committee. An NCRR Grants Management Specialist also may be present at the site visit to provide assistance to reviewers. In addition, a member of NCRR's DCRR staff usually attends the site visit as an observer and, when called upon by the SRA, serves as an information resource on interpretation of program policies for the members of the site-visit team.

At an executive session at the beginning of the site visit, the site visitors discuss the agenda, address potential concerns raised in their preliminary reviews of the submitted application, including human subjects issues in the protocols, and may ask the SRA to request specific documents (e.g., patient consent forms, correspondence, and other industry-related research documents) or to make arrangements to meet with any GCRC staff member or protocol investigator.

B. Site-Visit Agenda:

The following is a typical site-visit agenda for most GCRCs.

DAY 1 (on site):

7:00 a.m.	Meet in lobby of hotel for transportation to the site.
7:45 a.m.	Preliminary executive session of site visitors.
8:15 - 10:45 a.m.	Presentation by PD and others (see below)

10:45 - 11:00 a.m.	Break
11:00 a.m.	Administrative meeting of administrative reviewer with institutional officials (concurrent with scientific presentations).
11:00 - 11:30 a.m.	Scientific Presentation #1
11:30 - 12:00 noon	Scientific Presentation #2
12:00 - 12:30 p.m.	Scientific Presentation #3
12:30 - 1:15 p.m.	Lunch with applicant team
1:15 - 2:00 p.m.	Tour of Facilities
2:00 - 2:30 p.m.	Scientific Presentation #4
2:30 - 3:00 p.m.	Scientific Presentation #5
3:00 - 3:30 p.m.	Scientific Presentation #6
3:30 - 4:00 p.m.	Scientific Presentation #7
4:00 - 4:15 p.m.	Break
4:15 - 6:30 p.m.	Executive Session 2

DAY 2 (off site):

7:30 - 11:30 a.m.	Executive Session 3

C. Program Director and Infrastructure Presentations:

The two-and-a-half hours (8:15 a.m. - 10:45 a.m.) allowed for presentations by the PD and others is usually begun by a short presentation by the GCRC PI; there may be other introductory speakers (e.g., CEO of the Hospital, Vice-Chancellor of the University, elected officials), but it is suggested that these presentations be limited to a total of 10 minutes. The PD (with assistance from the Associate PD, GAC Chairperson, RSA, Core Laboratory Director, Informatics Core Manager, and other members of the GCRC staff, as desired) should use the remaining time to cover the following topics: Accomplishments; GCRC resources utilized since the last review; Response to critique in previous summary statement; Innovations since last review; Satellites; Core Laboratories; Biostatistics; Nursing; Patient Care; Bionutrition; Informatics; Training and Career Development; Center

Management; RSA; Justification for current request; GAC; IRB; Physical Facility; DSM Plan; and CReFF funds. All the above issues should be addressed; however, the PD may choose to arrange these presentations in a fashion that he/she believes will best highlight this GCRC, including the order, timing, and individual chosen to address a given topic, and with the option to reserve some of this time for a wrap-up session prior to the second executive session at the end of the first day. Adequate time after each presentation or group of presentations should be left for questions from the site visitors.

D. Scientific Content:

1. Project presentations are to be hypothesis-oriented and include justifications for GCRC resources requested for carrying out the studies.

2. Scientific presentations are limited to 15 minutes, allowing an additional 15 minutes for discussion by the site visitors with the presenting investigators.

3. Presentations may begin with a brief review of previous work (no more than 3-5 minutes) but should proceed rapidly to a clear statement of the questions proposed for future investigation. The experimental protocol should be described in some detail. Each presentation should consist of a description of how the GCRC will be used for the research project, a justification for requested resources (e.g., number of research patient days or visits by category, Informatics Core, etc.), and preliminary data.

4. For each presentation, reviewers will evaluate the scientific merit of the project and its need for inpatient days, outpatient visits, laboratory, Informatics Core, bionutrition research, nursing, and any other GCRC resources. In addition to asking questions about projects that are presented, reviewers may question investigators about their other projects described in the application that were not presented.

During the scientific presentations, the administrative consultant will meet with institutional representatives, the GCRC Administrative Manager, Nurse Manager, Bionutrition Research Manager, and any other relevant GCRC staff.

E. Executive Sessions:

At the beginning of each executive session, the site-visit SRA and the Chairperson brief the site visitors on their responsibilities and answer any questions the team members may have. Site visitors may request additional information from the PD, through the site-visit SRA.

In the second executive session on the afternoon of the first day (on site), primary reviewers of presented projects will read their critiques, including their evaluations of scientific merit and need for the GCRC resources. Following these presentations and discussion, each reviewer will numerically score (in a closed ballot, using the numerical ranges described

below) each of the presented projects, both for "Scientific Merit"and "Need For The GCRC." If questions arise during this executive session, a meeting may be required with the PD, administrative staff, or investigators (who may or may not have given presentations); all should remain available until the site-visit team leaves.

In the third executive session on the morning of the second day (which is held off site), the infrastructure sections including Program Directorship, GAC, and Core Laboratories (listed on page III-12) are discussed and evaluated by a process resulting in adjectival descriptors for each element. The site visitors then collectively make their recommendations on each of the items requested in the budget: inpatient days and outpatient visits (Categories A and B), grant-supported positions, equipment, supplies, renovations, etc. In addition, site visitors may be assigned protocols to review that are not presented at the site visit. Written comments for the protocols not presented are required from the assigned site visitor only if there are human subjects protections issues and/or women/minority/children inclusion issues. The PD and Administrative Director should be available to address any questions raised during the third executive session.

IV. RESPONSIBILITIES OF THE SITE-VISIT CHAIRPERSON

The Chairperson of the site-visit team, usually a member of the Clinical Research Review Committee, should be a senior clinical investigator experienced in the review of complex multidisciplinary applications and generally knowledgeable in the scientific areas to be reviewed. When there is to be no subsequent review by the Clinical Research Review Committee, due to conflict of interest or other reasons, the site-visit team will constitute a SEP, and the site-visit Chairperson becomes the Chairperson of the SEP. In this case, the Chairperson cannot be a member of the CRRC. It is expected that the Chairperson is to become thoroughly familiar with the entire application prior to coming to the site visit.

During the presentations at the open sessions of the site visit, the Chairperson moderates the flow of the presentations, makes sure that the presenters adhere to the predetermined schedule, and assures that the presenters leave adequate time for questions. At the end of each presentation, the Chairperson invites the members of the site-visit team to address questions to the presenter on issues that need further clarification. The site visitors should be thorough in their efforts to obtain all information necessary for adequate evaluation of the proposal. The Chairperson is to ensure that, at all times, the site visit remains a friendly, non-adversarial, fact-finding mission.

During the concluding executive session of the site visit, the Chairperson moderates the discussion on the scientific presentations and on various programmatic issues and decides when to limit additional discussion on each topic and proceed to scoring or voting. The Chairperson or administrative reviewer leads the discussion on the budget, assuring that recommended deletions from the requested budget are justified.

V. PREPARATION OF REVIEWS OF SCIENTIFIC PRESENTATIONS

Reviews of all projects presented at the site visit should be written in a uniform format. Additionally, each project receives two priority scores. The first priority score reflects the scientific merit, and the second, the need for GCRC resources. The projects presented at the site visit are chosen by the PD and should reflect a significant portion of the resources requested within the GCRC application.

Each of the presented projects will be reviewed individually, and the assigned reviewer(s) will read his/her critique of the project in the second executive session at the end of the first day. Assigned reviewers should prepare their initial reports prior to the site visit. The reports should be edited and modified as necessary to reflect the site-visit team's evaluation and recommendations. The written summary, in the format described below, should be completed and given to the SRA at the close of the site visit in hard copy as well as on a disk in Microsoft Word.

FORMAT FOR SCIENTIFIC PROJECT REVIEW

A. Protocol Title:

B. Investigator Name(s):

C. Summary of Investigator Credentials: Describe the professional background and training of investigator(s), publications in peer-reviewed journals, and current research grant support. Are the investigators appropriately trained and well suited to carry out this work? Is the proposed work appropriate to the experience level of the PI and other researchers (if any)? Does the investigative team bring complementary and integrated expertise to the project?

D. Summary of Proposal: You need not supply a summary of the proposal, as the abstract supplied in the grant application will be inserted into the final summary statement. However, if there are major changes in the project as presented at the site visit compared to that in the grant application, the reviewer should add text indicating the changes.

E. Critique: Provide a detailed narrative based upon the written proposal and the additional information obtained at the site visit. Do not include questions in your critique; any questions you have should be asked during the site visit and your evaluation of the answers included in your written review. In preparing your evaluation, please be concise; address all issues in the third person; state what is missing and what remains unclear; and avoid any use of pejorative language. If, in your preliminary evaluation, you have noted deficiencies in the proposal or issues requiring clarification that are dealt with adequately during the site visit, you should modify this portion of your review to reflect the new information. Please address, in individual sections, the criteria listed below. Under each criterion are sample questions. These are examples only, and you need not feel constrained to address each

query or to limit your review to these questions. Plans for data sharing or HIPAA compliance are not reviewed. (See NOT-OD-03-025.)

1. Significance
   Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

2. Approach
   Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation
   Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

4. Environment
   Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

5. Overall Evaluation
   Briefly summarize the strengths and weaknesses of the protocol and recommend an overall level of merit, weighting the above criteria as you feel appropriate.

F. Protocol Scientific Recommendation: The scientific merit of the proposal is the major determinant in the assignment of a score. The prior accomplishments of the investigator, although an important factor, do not justify a high level of enthusiasm for projects with serious scientific deficiencies. A protocol does not need to be strong in all categories to be judged likely to have major scientific impact. Furthermore, an investigator may propose to carry out important work that is not inherently innovative; however, it may be essential to move a field forward. The recommendation should be a numerical score ranging between 1.0 and 5.0 (1.0 being the best) or, if the proposal does not have substantial and significant merit or poses gravely hazardous conditions, a motion may be entertained for "not recommended for further consideration."

G. Need For The GCRC: Here, use a numerical score related to one of the descriptors listed

below in your recommendation.

Descriptor	Numerical Range
Cannot be carried out without Center resources	(1.0 - 1.5)
Unlikely to be carried out without Center resources	(1.6 - 2.5)
Could possibly be conducted off-Center, but Center resources would facilitate study	(2.6 - 3.5)
Minimal need for Center resources	(3.6 - 5.0)
No apparent need for Center resources	(No Score)

H. Human Subjects Issues: Indicate whether any additional restrictions or clarifications for patient enrollment in the proposed study should be considered, and whether risk-benefit or ethical issues exist. If none exist, state so specifically. Reviewers should examine consent forms. NIH recently redefined a Human Subject Concern as follows: "A human subject concern is defined as any actual or potential unacceptable risk, or inadequate protection against risk, to human subjects as described in any portion of the application." (See the NIH Instructions to Reviewers for Evaluating Research Involving Human Subjects in Grant and Cooperative Agreement Applications.)

I. Inclusion of Women, Minorities, and Children: Indicate whether inclusion of women, minorities, and children is properly addressed in the project, and provide the appropriate codes.

GENDER CODE	MINORITY CODE	CHILDREN CODE
First Character: G	First Character: M	First Character: C
Second Character	Second Character	Second Character
1=both genders	1=minority and nonminority	1=both children and

2=only women	2=only minority	adults
3=only men	3=only nonminority	2=only children
4=gender unknown	4=minority representation unknown	3=no children included
		4=representation of children unknown
Third Character	Third Character	Third Character
A=scientifically acceptable	A=scientifically acceptable	A=acceptable
U=scientifically unacceptable	U=scientifically unacceptable	U=unacceptable

J. Animal Use Issues: If animals are involved, state whether their use and care are appropriate for the proposed studies.

K. Summary of Resources Requested and Recommended: Provide a summary of the resources requested by the investigator (category A and/or B inpatient days and/or outpatient visits, Core Laboratory usage, etc.), and your judgment of what is needed. For industry-related projects, state whether the study is investigator-initiated or industry-initiated.

Important Note: At the site visit, you should modify the review you wrote prior to coming to the site visit to take into account additional information presented at the site visit, as well as the discussion and consensus of the site-visit team. Please edit your written review accordingly, and give it to the SRA by the close of the meeting on the second day. Provide the SRA with a "hard copy" of the critique and an electronic copy on a disc in Microsoft Word.

VI. PREPARATION OF REVIEWS OF ADMINISTRATION AND INFRASTRUCTURE

The administrative reviewer of the GCRC site-visit team should use the following format to prepare the written critique for the site visit. You are requested to write up the following sections: A. BACKGROUND; B. ORGANIZATION AND ADMINISTRATION; C. NURSING; D. BIONUTRITION RESEARCH (if support is requested in the application); and E. PHYSICAL FACILITY. Other members of the site-visit team will provide evaluation of: F. PROGRAM DIRECTORSHIP; G. ACCOMPLISHMENTS; H. GAC; I. IRB; J. PATIENT CARE; K. TRAINING AND CAREER DEVELOPMENT; L. CORE LABORATORY; M. BIOSTATISTICS; N. INFORMATICS CORE; O. DATA AND SAFETY MONITORING PLAN; P. CLINICAL RESEARCH FEASIBILITY FUNDS; and Q. RESEARCH SUBJECT ADVOCATE. Each of these categories is reviewed according to the instructions given below and given a verbal descriptor. The list of descriptors and corresponding priority scores is:

Descriptor	Numerical Range
Outstanding	(1.0 - 1.5)
Excellent	(1.5 - 2.0)
Very good	(2.0 - 2.5)
Good	(2.5 - 3.5)
Acceptable	(3.5 - 5.0)

A. BACKGROUND (Not to exceed a single-spaced page)

This section should briefly, but accurately, describe the following: 1.) organizational structure of the institution (e.g., medical school, hospital); 2.) the relationship of the institution to the state or local government (if appropriate), or its relationship to any other entity; 3.) institutional chain of command; 4.) the different types of health-related professional schools; 5.) the approximate size of the faculty; 6.) the types of degrees the medical school offers (M.D., Ph.D., M.D./Ph.D., etc.); 7.) the number of students, fellows, interns, etc., being trained; 8.) the number of beds and bed occupancy of the hospital(s); 9.) the administrative and financial structure of the institution; and 10.) the administrative lines of responsibility, as related to the administration of the GCRC grant. Describe the financial structure: Medicare, Medicaid, private patient income, etc.

Briefly describe the history of the GCRC. Mention administrative changes (PI, PD, etc.) since the last review of the GCRC, and particularly note changes made in response to critiques of the previous review.

B. ORGANIZATION AND ADMINISTRATION

Administration and Financial Management: Briefly describe the lines of responsibility concerning administrative matters within the Institution and GCRC. If there are separate units, such as separated inpatient and outpatient units, list these and give name and rank of persons in charge. Discuss financial management within the Institution and GCRC: 1.) office responsible for the preparation of the proposed patient care rates; 2.) office responsible for the preparation of the financial status reports; 3.) persons responsible for the authorization of grant expenditures and verification of the charges to the grant; 4.) patient bills; 5.) costs by project; 6.) verification and control of charges to grant; 7.) involvement in budget preparation for application; 8.) review of routine cost stepdown in patient care rates; 9.) census data records by category: A, B, C, D inpatient days, outpatient visits, scatter-bed days; 10.) records for annual and expenditure report requirements; and 11.) classification of inpatient days and outpatient visits along with the appropriate designation of patients to categories.

C. NURSING

Evaluate whether the requested number of nursing personnel is justified on the basis of the number and intensity of research projects. Your evaluation should include the following: 1.) relationship between the hospital nursing administration and the GCRC nursing staff; 2.) evaluation of the Head Nurse/Nurse Manager; 3.) stability of the staff; 4.) involvement of nurses in practical aspects of project planning and in nursing research; 5.) staffing patterns; 6.) extent of weekend research activity on the GCRC; 7.) source of staff coverage for leave and holidays; 8.) nursing student training; 9.) number of nurses required for outpatient or scatter-bed activities; 10.) nursing care required by research subjects and category C and D patients, severity of patient illness, and extent of special nursing problems: children, transplant subjects, acutely ill subjects, patients in isolation, etc.; and 11.) adequacy of current number and qualifications of nursing staff and recommendation for requested increments in nursing positions.

D. BIONUTRITION RESEARCH (if support is requested in the application)

Not all GCRCs require a Bionutrition Core. When present, it facilitates and implements the nutrition components of GCRC protocols. It may be involved in one or more of the following functions: assisting investigators with nutrition aspects of research design, implementation, data collection and analysis; implementing controlled feeding studies (via meals prepared on site or outsourced as appropriate) and metabolic studies, as well as facilitating and monitoring subject nutrition compliance; performing nutrition and nutrient intake assessment; conducting anthropometric, body composition, calorimetry and other physiologic and metabolic measurements; providing personnel administration, metabolic kitchen operations, food procurement, production and service; and educating and training professional and non-professional staff, study participants, students and the public.

The review should address the following: 1.) utilization of the Bionutrition Core's services, including future directions and requests; 2.) the roles, qualifications, training, and adequacy of current, and requested staffing; 3.) adequacy of space and equipment to carry out the services requested; 4.) plans to assure quality assurance activities, as well as record keeping; 5.) relationships between the GCRC Bionutrition staff and the departments and other entities, both within and outside of the institution, used for procurement of foods, staffing, or other resources, as well as with other GCRC staff; 6.) involvement of the Bionutrition staff in the education and training of dietetic interns and other health professionals; and 7.) participation of the Bionutrition staff in the development of GCRC protocols, and other research activities.

E. PHYSICAL FACILITY

Evaluate the configuration of the space on the GCRC needed to implement the scope of research activities recommended. Your evaluation must include considerations for outpatient use as well as inpatient use, computing facilities, and all other space on the GCRC. Note changes that were made in the physical facility of the GCRC since the last

review, and describe the general appearance of the GCRC and ways in which its configuration or maintenance may need to be improved.

Assess the most cost-effective configuration of the GCRC *vis a vis* the site-visit recommendation for inpatient research days and outpatient visits, taking into account the complexity of the proposed research for proposals of high scientific merit and the suitability of the facility considering the level of illness of research patients and the age groups studied (e.g., infants, adolescents, the aged). Review the list in the application detailing use and square footage of each room/area proposed for the GCRC and areas that will not be charged to the grant. Review the proposed list of rooms to be used for inpatient and for outpatient studies. Assess efficiency of the configuration *vis a vis* the projected number of visits, length of visits, average number of hours per day and days per week. If the proposed configuration is not congruent with the resource needs projected by the site-visit team's recommendation for inpatient research days and outpatient visits, this should be noted in your review.

Unless otherwise justified, a unit funded under the discrete funding mechanism should be within the main patient-care area of the hospital, close to the administrative offices of the PD and Administrative Manager. The RSA office should be close to the patient-research area to facilitate access to the unit and to facilitate interaction with GCRC staff and research participants. The Informatics Core area should be convenient and efficient, with terminals readily accessible to investigators. The Core Laboratory should be an appropriate size for its function.

If alterations and renovations are requested, provide an explanation for these and make recommendations to the site-visit team on the justification or the need of the GCRC for these alterations and renovations.

Review all requests for equipment and for supplies, and provide an explanation for the recommended changes.

F. PROGRAM DIRECTORSHIP

The PD should be an individual with relevant knowledge, scientific expertise, and evidence of administrative skills. In addition, the PD should be involved in the conduct of GCRC-based research and be a recipient of independent, peer-reviewed research funding. Associate and Assistant PDs are active investigators at the GCRC and recipients of peer-reviewed funding as PIs or co-investigators. PDs and Associate PDs must be licensed physicians. The PD ultimately is responsible for the day-to-day oversight of GCRC activities.

The site visitor assigned primary responsibility for reviewing Program Directorship should describe the professional background of the PD, Associate Director(s) and/or Assistant

Director(s): training, publications in peer-reviewed journals, current research funding, history of demonstrated scientific and administrative leadership, and the extent to which GCRC resources are used. For each individual, detail administrative functions on the GCRC, and evaluate the appropriateness of the proposed effort (fraction of FTE).

G. ACCOMPLISHMENTS

This section is written only for GCRC renewals and not for new GCRC applications. Highlight major scientific accomplishments of the GCRC since the last competitive renewal. Accomplishments selected should represent advances or achievements that led to the prevention of disease, provided a better understanding of a disease process or of a physiologic mechanism, provided a new or better therapeutic approach, or resulted in a new methodology for the early detection or diagnosis of disease. The narrative should make clear the nature of each accomplishment, its originality, and its significance, as well as the GCRC support that was provided for these studies (days, visits, core laboratory, etc.). State if the accomplishment has found application in the health care system. Describe any findings that result in more cost-effective approaches to diagnosis or therapy. Did the Bibliography section of the application properly indicate publications that cited the GCRC grant?

H. GAC

Describe the makeup and functioning of the GAC. At the site visit, review the minutes of recent GAC meetings. Prepare your critique of the GAC addressing the following issues:

1. Are the GAC minutes complete and informative?

2. Are GAC meetings held regularly and is attendance adequate?

3. Is the GAC operating properly, i.e., :

- approving projects before they begin
- classifying projects as category A, B, or D, especially industry-related projects
- assuring implementation of NIH policy on the inclusion of women, minorities, and children as study subjects
- evaluating risk-benefit, ethics, and safety
- approving DSM plans
- overseeing the Core Laboratories

- setting Center policies
- overseeing the GCRC budget?

I. IRB

Describe the makeup and functioning of the IRB. At the site visit, review minutes of recent IRB meetings and consent forms. Are the minutes complete and informative? The minutes should document significant issues discussed and not simply state "approved," "deferred," or "rejected." Are meetings held regularly? Is attendance adequate? Is the IRB often requiring changes in proposed protocols and/or consent forms submitted for its review? Are the consent forms adequate? Discuss the IRB and GAC processes, including usual time required for protocol approval.

J. PATIENT CARE

Delineate responsibilities for medical care delivery by investigators and oversight of medical care by the PDs. Describe the role of interns, residents, and fellows in patient care and emergency coverage. At the site visit, inspect some patient charts and comment on the adequacy of chart entries, including records of histories and physical examinations and inclusion of progress notes. The presence of signed consent documents in the GCRC administrative or research files on the unit should be evaluated.

K. TRAINING AND CAREER DEVELOPMENT

The training of health professionals in the methods of clinical investigation should be an integral part of the research effort on every GCRC. The GCRC should provide a major local institutional focus for training in clinical research methodology, bioethics, biostatistics, clinical trial design, epidemiological studies, and other methods, including basic laboratory methods. Formal courses may be set up for this goal and may include NRSA fellows and trainees as well as K23 awardees, and junior faculty. Regular rotation on the GCRC by research fellows, house officers, and medical, nursing, and dietary students is encouraged. Because GCRCs are expected to represent models of excellence in contemporary clinical research techniques, they also may be used for other instructional purposes, including programs of continuing education for practicing physicians, nurses, and dietitians. If the institution has received a K30 or K12 award, describe how the GCRC is involved.

Describe the accomplishments and plans of the GCRC as a training resource for CAPs, MCAPs, K23s, medical students, house officers, fellows, faculty, nurses, and dietitians.

L. CORE LABORATORIES

The Guidelines for the GCRC Program state that the primary functions of a Core Laboratory are the support of ongoing GCRC clinical research and the development or validation of new methods for this purpose; it also may include clinical research training of investigators, fellows, students, and technicians. Not all GCRCs need a Core Laboratory. Sometimes, the only requirement is for a small sample-processing area.

In general, routine blood chemistries, hematologic determinations, and urinalyses that are available in the hospital's clinical chemistry laboratories or in another Medicare-approved clinical chemistry laboratory are not supported in the GCRC Core Laboratory; rather, they are paid as ancillaries. However, such tests may be supported in the GCRC Core Laboratory when this is important for patient safety, timeliness, or accuracy, which could affect the scientific quality of the results.

Prepare your critique of the Core Laboratory addressing the following issues:

1. The utility of the Core Laboratory as a resource for a wide spectrum of clinical research by GCRC users. Number of investigators using the GCRC and number using the Core Laboratory. Is there dominance of Core Laboratory usage by only one or two investigators or groups?

2. The justification for a Core Laboratory in terms of collective needs and cost. Cost effectiveness, *per se*, does not provide justification of a Core Laboratory or any of its separate functions and components.

3. The scientific merit of projects and availability of peer-reviewed funding of investigators using or requesting Core Laboratory function and activities.

4. The types of laboratory determinations to be performed. How decisions are made as to which analyses will be performed.

5. The role, qualifications, and FTEs requested for the Core Laboratory Director and technical staff. Justification for level of effort in terms of Core Laboratory function and complexity.

6. The performance of the Core Laboratory to date, and its proposed future direction as influenced by expected changes in GCRC activity. Its use for training of clinical investigators, students, fellows, and technicians.

7. The adequacy and appropriateness of space and equipment to carry out the work.

8. The availability of Standard Operating Procedures and adequacy of record keeping, confidentiality, and quality-control procedures. Is the CLIA certification status of the Core Laboratory appropriate to the work being conducted?

9. Is there any intermingling of personnel, space, or equipment of the Core Laboratory with other laboratories, such as the GCRC Program Director's research laboratory or the hospital's clinical chemistry laboratory? Can those activities be identified and appropriate charges made?

10. Is there appropriate reimbursement to the GCRC grant for tests supported by investigators'' peer-reviewed funding? (Reimbursement is transferred to the patient-care category of the GCRC grant.)

M. BIOSTATISTICS

Is there a Biostatistician (with proper qualifications) funded by the GCRC grant? Is he/she a member of the GAC, and does he/she review all projects before they are approved to begin on the GCRC? Do the projects presented at the site visit document proper statistical design, including appropriate power calculations, sample sizes, and stratifications?

N. INFORMATICS CORE

1. Evaluate the scientific merit of GCRC projects using Informatics Core and evidence of peer-reviewed funding of protocol investigators.

2. Evaluate the reasonableness of proposed hardware configuration in light of GCRC size and anticipated investigator use and the plans to accommodate growth or extend usefulness (e.g., local area network within GCRC or institution). Is it/will it be cost-effective?

3. Comment on location of the resource. Include comments on access to the Informatics Core by staff and to the Informatics Core Manager for help on technical problems.

4. Comment on whether appropriate quality control of data acquisition and data maintenance is employed. Is data security in place, and is it adequate? [Note that an evaluation of compliance with the HIPAA Privacy Rule or plan for data sharing are not part of the peer review of any application to NIH.]

5. Evaluate evidence of appropriate utilization of the system and rationale for requested changes. Are data storage and analysis appropriate?

6. Determine if there is review and oversight by the GAC for utilization of the Informatics Core resource. Is there evidence that the Informatics Core Manager and the Biostatistician have input into project review for needs assessment (e.g., statistical analyses, requisite software)?

7. Identify investigators and individuals with hands-on experience.

8. Comment on utilization for collaborative investigations or registries.

9. Evaluate the extent to which the Informatics Core is used for non-GCRC-based studies and whether these studies are related to ongoing or proposed research projects at the GCRC.

10. Define the role of the Informatics Core Manager and the expertise required to implement/support systems at the GCRC.

O. DATA AND SAFETY MONITORING PLAN

Evaluate the overall DSM Plan of the GCRC, including: Will there be an approved DSM plan for each GCRC protocol before the protocol begins? Are procedures in place for ensuring that all protocols that place participants at significant risk have included a DSMB? Evaluate the policies and procedures of the GCRC for establishment, implementation, oversight, and continuing review of protocol DSM plans. Evaluate the procedures of GCRC for monitoring and handling of adverse events and serious adverse events that occur on GCRC protocols. Evaluate the appropriateness and merit of at least three of the individual DSM plans. The DSM plans for each of the protocols in the application shall be available for review either in the application or at the site visit.

P. CLINICAL RESEARCH FEASIBILITY FUNDS

Is there a request for a CReFF Program? If so, comment on the guidelines for eligibility, selection criteria, and evaluation of the program. If the CReFF Program has been in existence, comment on its accomplishments to date.

Q. RESEARCH SUBJECT ADVOCATE

Based on the written material in the application and the presentation at the site visit, evaluate the effectiveness of the RSA program as implemented at the GCRC in promoting research participant safety. Evaluate the qualifications, proposed effort, and division of responsibilities of the RSA personnel. Discuss the appropriateness and effectiveness of the reporting arrangements of the RSA(s). Evaluate the appropriateness and value of the activities and responsibilities of the RSA(s) as described in the application and at the site visit, including but not limited to: consultation with and education of the GAC, PD, investigators, nurses, laboratory and other core personnel related to human subjects protection issues on the GCRC; counseling research participants; DSM plans; safety monitoring, including adverse events/serious adverse events; policies and procedures for protection of human subjects on the GCRC; and liaison with institution human subjects protection offices, including IRBs.

VII. STRENGTHS AND WEAKNESSES

The Chairperson of the site-visit team will compile a summary listing of the GCRC application's strengths and weaknesses and discuss it with the entire site-visit team for concurrence at the end of the third executive session on day two.

A. Typical strengths of a highly rated GCRC application may include the following:

Hypothesis-oriented projects of high scientific merit and strong biostatistical design, with demonstrated need for the GCRC; a substantial number of investigators receiving peer-reviewed grants from Federal agencies; publication of research findings in high-quality, peer-reviewed journals; evidence of multidisciplinary research among both basic and clinical departments; a balance of senior and junior investigators; effective efforts to encourage and promote career development of junior clinical investigators; scientifically and administratively strong PD; good institutional support to the GCRC, Core Laboratory, and Informatics Core used by a large number of investigators and projects; well-trained and effective nurses and bionutrition research staff; functional and attractive physical facility; unique patient populations; and positive response to weaknesses in past review.

B. Typical weaknesses of a GCRC application may include the following:

Minimal peer-reviewed grant support to GCRC investigators; several projects with serious scientific flaws; inadequate biostatistical input to projects; several projects with no demonstrated need for the GCRC; many papers by investigators proposing to use the GCRC published in journals not subjected to critical peer review; domination of the GCRC by one research group; many projects are descriptive rather than hypothesis testing; poor utilization of outpatient facility and research beds; inadequate correction of weaknesses cited at the previous review; few investigative groups active in research; institution not supportive of the GCRC; deficiencies in physical facility; lack of supervision of junior physician-investigators; application or site visit not well prepared; PD not actively involved in research and not independently funded; inadequately functioning local GAC and/or IRB; GCRC not used well for training; and inadequate inclusion of women, minorities, and children in projects.

VIII. SUMMARY AND RECOMMENDATIONS

The Chairperson will entertain a motion for not recommending the application for further consideration. In the absence of such a motion, or if the motion is not carried, the Chairperson will entertain a motion for the number of years recommended for support. The majority vote carries in each case. For a SEP, if there is a split vote (two or more votes of dissent) with regard to not recommending the application for further consideration, a minority report shall be prepared. If the site-visit team is a SEP, all of the reviewers record a final priority score for the GCRC; otherwise, the CRRC will assign the final priority score.

The team then will discuss the budgetary recommendation for the GCRC. Reviewers should provide an explanation for any reduction or deletion in the requested budget. Should there be a difference of opinion, the majority vote carries.